CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Open Label Study to Evaluate the Efficacy and Safety of Tenofovir Alafenamide (TAF) versus Tenofovir Disoproxil Fumarate (TDF)–containing Regimens in Subjects with Chronic HBV Infection and Stage 2 or Greater Chronic Kidney Disease Who Have Received a Liver Transplant	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
Indication:	Chronic Hepatitis B	
Protocol ID:	GS-US-320-3912	
Gilead Study Director:	Name: Telephone: Fax:	PPD PPD PPD
	Name: Telephone: Fax:	PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3:	07 June 2016 22 November 2016 28 March 2017 18 June 2019

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 2, Randomized, Open Label Study to Evaluate the Efficacy and Safety of Tenofovir Alafenamide (TAF) versus Tenofovir Disoproxil Fumarate (TDF)–containing Regimens in Subjects with Chronic HBV Infection and Stage 2 or Greater Chronic Kidney Disease Who Have Received a Liver Transplant
Clinical Trials.gov Identifier:	NCT02862548
Study Centers Planned:	Approximately 1 center in New Zealand
Objectives:	The primary objectives of this study are as follows: • To evaluate the safety and tolerability of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in $eGFR_{CKD-EPI}$ at Week 24 • To evaluate the efficacy of TAF 25 mg QD versus TDF-containing regimens in maintaining viral suppression at Week 24 The secondary objectives of this study are as follows: • To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the percent change from baseline in hip and spine bone mineral density (BMD) at Weeks 24 and 48 • To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in serum creatinine at Weeks 24 and 48 • To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in $eGFR_{CKD-EPI}$ at Week 48 • To evaluate the efficacy of TAF 25 mg QD versus TDF-containing regimens in maintaining viral suppression at Week 48

The exploratory objectives of this study are as follows:

[redacted]

Study Design:

This is a randomized, open-label, single center Phase 2 study to evaluate the safety and efficacy of TAF 25 mg QD versus TDF in adult chronic hepatitis B infection (CHB) subjects with Stage 2 or greater chronic kidney disease and have received a liver transplant.

Approximately 50 subjects will be randomized in a 1:1 ratio to either continue current treatment regimen with TDF alone or in combination with other approved antivirals or to receive TAF 25 mg PO daily. Approximately 40 of 50 subjects will be enrolled with $eGFR_{CKD\text{-}EPI} < 60$ ml/min/1.73m^2.

Randomization will be stratified by baseline renal function ($eGFR_{CKD\text{-}EPI} < 50$ ml/min/1.73m^2 and ≥ 50 ml/min/1.73m^2)

- **Treatment Arm A:** approximately 25 subjects administered TAF 25 mg oral daily
- **Treatment Arm B:** approximately 25 subjects to continue administration of TDF alone or in combination with other approved antivirals as per local practice

CCI [redacted]

The primary analysis will occur at Week 24 with the primary efficacy endpoint being the maintenance of viral suppression (HBV DNA < 20 IU/mL).

	CCI [redacted]
Number of Subjects Planned:	Approximately 50
Target Population:	Adult subjects with CHB who are currently virally suppressed, receiving TDF alone or in combination with other approved antivirals as per local practice, with Stage 2 or greater chronic kidney disease and have received a liver transplant.
Duration of Treatment:	TAF will be administered orally once daily for 48 weeks for subjects in Treatment Arm A. Subjects in Treatment Arm B will continue on TDF alone or in combination with other approved antivirals. CCI [redacted]
Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria** Subjects must meet **all** of the following **inclusion criteria** to be eligible to participate in the study: 1) Must have the ability to understand and sign a written informed consent form; consent must be obtained prior to initiation of study procedures 2) Adult male or non-pregnant female subjects, over 18 years of age based on the date of the screening visit 3) Documented evidence of chronic HBV infection prior to transplantation 4) Primary or secondary (re-transplant), liver alone or liver and kidney transplant recipient from deceased or living donor 5) Liver Transplant ≥ 12 weeks prior to screening 6) Maintained on TDF alone or in combination with other approved antivirals for HBV prophylaxis or treatment 7) Have been on approved HBV OAV treatment for at least 12 weeks post-transplant prior to screening, with HBV DNA < LLOQ at screening

8) Screening $eGFR_{CKD-EPI}$ < 90 ml/min/1.73m^2
9) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 6
10) Women considered of child bearing potential (see Appendix 6) must have a negative serum pregnancy test at Screening and a negative urine test at Baseline before dosing
11) Must be willing and able to comply with all study requirements

Exclusion Criteria

Subjects who meet **any** of the following **exclusion criteria** are not eligible to participate in the study:

1) Multi-organ transplant that includes heart or lung recipient (subjects who have their liver transplant as part of a liver-kidney dual transplant are eligible to enroll)
2) Subjects with history of de novo or recurrent hepatocellular carcinoma (HCC) post-transplant and at screening
3) Histological evidence of unresolved transplant rejection
4) Current, uncontrolled ascites, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, or other signs of decompensated cirrhosis
5) Subjects meeting any of the following laboratory parameters at screening:
    a) ALT > 10× the upper limit of normal (ULN)
    b) INR > 1.5 × ULN unless the subject is stable on anticoagulant regimen affecting INR
    c) Albumin < 3.0 g/dL
    d) Direct bilirubin ≥ 4 × ULN
    e) Platelet count < 50,000/mL
    f) $eGFR_{CKD-EPI}$ < 15 ml/min/1.73m^2
6) Subjects on hemodialysis
7) Co-infection with HIV or HCV
8) Recent (within 4 weeks of Screening) episode or infection requiring systemic antibiotics
9) Use of any prohibited medications listed in Section 5.4 within 28 days of the Baseline/Day 1 visit

10) Malignancy within 5 years prior to screening, with the exception of specific cancers that are cured by surgical resection (e.g., basal cell skin cancer, etc.) or hepatocellular carcinoma. Subjects under evaluation for possible malignancy are not eligible
11) Significant cardiovascular, pulmonary, or neurological disease
12) Use of investigational agents within 3 months of screening, unless allowed by the Sponsor
13) Use of any prohibited medications as described in Table 5-1
14) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance
15) Known hypersensitivity to study drugs, metabolites or formulation excipients
16) Lactating females or those who may wish to become pregnant during the course of the study

Study Procedures/ Frequency:

- Screening Visit
- Treatment Period Visits: Baseline/Day 1, Weeks 4, 8, 12, 20, 24, 36, and 48
- [redacted]

Screening assessments include:

- Safety laboratory tests (chemistry, hematology, and coagulation)
- HBV DNA levels
- HBV serology (qualitative HBsAg, and qualitative HBeAg; HBeAb and HBsAb reflex testing will be performed as needed)
- HCV, HDV and HIV testing
- Alpha-fetoprotein (AFP)
- $eGFR_{CKD\text{-}EPI}$
- Hip and Spine DXA Scan
- Urinalysis, urine drug screen
- Serum beta human chorionic gonadotropin (β-hCG, for all female subjects of child-bearing potential)
- Physical examination (with height and body weight), medical history, vital signs, concomitant medications, and adverse events

On-treatment assessments include:

- Safety laboratory tests (chemistry, hematology, and coagulation),urine pregnancy tests (for all female subjects of child-bearing potential), urinalysis, physical examination (with weight), vital signs, concomitant medications, and adverse events
- Serum Renal Biomarkers including phosphate, Cystatin C at Baseline, Weeks 4, 12, 24, 48 , Early Discontinuation (ED), CCI [redacted]
- Urine Biomarkers e.g., total protein, creatinine, albumin, retinol binding protein, beta-2 microglobulin, uric acid and phosphate at Baseline, Weeks 4, 12, 24, 48, ED, CCI [redacted] nd ED Cr EDTA Renal Scan at Baseline, Week 48, CCI [redacted]
- Serum Bone Biomarkers including C-type collagen sequence, procollagen type 1 N-terminal propeptide, osteocalcin, bone specific alkaline phosphatase, and parathyroid hormone at Baseline, Weeks 4, 12, 24, 48, ED, CCI [redacted] and ED Hip and Spine DXA Scan at Screening, Weeks 24, 48, ED, CCI [redacted]
- Fracture Risk Assessment will be evaluated at Baseline
- HBV serology (qualitative HBsAg, and qualitative HBeAg; HBeAb and HBsAb reflex testing will be performed as needed) at Baseline and Weeks 24, 48, ED, CCI [redacted]
- HBV DNA levels at Baseline and at each study visit thereafter, CCI [redacted]
- PBMC specimens are collected at Baseline, Weeks 24, and 48
- Fibrotest® and vitamin D assessments at Baseline, Weeks 24, 48, ED, CCI [redacted]
- Serum storage for potential resistance testing (sequencing and phenotypic analyses) at Baseline and at each study visit thereafter, CCI [redacted]

- Health Related Quality of Life (HRQoL) Surveys (SF-36, CLDQ, and WPAI) at Baseline, Weeks 24, 48, ED, CCI [redacted]
- Single plasma PK samples at Baseline and at treatment visits through Week 48

CCI [redacted]

See Section 6 for further information.

Test Product, Dose, and Mode of Administration:	Open label TAF will be supplied as 25 mg tablets for daily oral administration with food
Reference Therapy, Dose, and Mode of Administration:	Open-label TDF alone or in combination with or without other antivirals administered per local practice

Criteria for Evaluation:

Safety:

Adverse events (AEs) and clinical laboratory tests will be collected at every visit throughout the study, CCI [redacted] he proportion of subjects in each treatment arm with an AE leading to early discontinuation of study drug(s) and proportion of subjects with serious adverse events will be summarized through Weeks 24, 48, CCI [redacted]

The **primary safety endpoint** is:

- Change from baseline in $eGFR_{CKD-EPI}$ of TAF 25 mg QD versus TDF-containing regimens at Week 24

The **secondary safety endpoints** are:

- Percent change from baseline in hip and spine bone mineral density (BMD) of TAF 25 mg QD versus TDF-containing regimens at Weeks 24 and 48
- Change from baseline in serum creatinine of TAF 25 mg QD versus TDF-containing regimens at Weeks 24 and 48
- Change from baseline in $eGFR_{CKD-EPI}$ of TAF 25 mg QD versus TDF-containing regimens at Week 48

Efficacy:	The **primary efficacy endpoint** is: • Proportion of subjects with HBV DNA < 20 IU/mL at Week 24 The **secondary efficacy endpoint** is: • Proportion of subjects with HBV DNA < 20 IU/mL at Week 48
Exploratory endpoints:	[redacted]
Pharmacokinetics:	All subjects will have single plasma PK samples drawn at each treatment visit through Week 48. At Weeks 8 and 24 the PK sample should be collected between 15 minutes and 4 hours post-dose. CCI [redacted]

Statistical Methods:	The primary analysis will be performed when the last subject has completed Week 24 assessments or discontinued prematurely. The response rate for each treatment arm will be summarized. A two-sided 95% confidence interval adjusted for the randomization stratification factor (the adjusted Mantel-Haenszel proportions), for the difference (TAF − TDF) in the proportion of subjects who maintained viral suppression (HBV DNA< 20 IU/mL) at Weeks 24, and 48 will be constructed. The change from baseline in $eGFR_{CKD-EPI}$ at Weeks 24, 48, CCI [redacted] will be summarized. The percent change from baseline in hip and spine BMD at Weeks 24, 48, CCI [redacted] will be summarized. The change from baseline in serum creatinine at Weeks 24, 48, CCI [redacted] will be summarized. All secondary continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum). All categorical secondary endpoints will be summarized by number and percentage of subjects who meet the endpoint.
Sample Size:	This is an exploratory study. No formal sample size calculation was performed.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	Degrees Celsius
°F	Degrees Fahrenheit
ADV	Adefovir dipivoxil
AE	Adverse event
AhR	Aryl hydrocarbon receptor
AK	Adenylate kinase
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AR	Adverse reaction
AST	Aspartate aminotransferase (SGOT)
AUC_{inf}	Area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0-last} + (C_{last}/\lambda_z)$
AUC_{tau}	Area under the plasma concentration versus time curve over the dosing interval (tau)
bsAP	Bone specific alkaline phosphatase
BMD	Bone mineral density
CatA	Cathepsin A
CD4	Cluster of differentiation 4 cells
CD8	Cluster of differentiation 8 cells
Ces1	Caboxylesterase-1
CHB	Chronic hepatitis B
CI	confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CL/F	Apparent oral clearance after administration of the drug
CL_{Cr}	Creatinine clearance
C_{max}	The maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
COBI/C	Cobicistat
CRF/eCRF	Case report form(s)/electronic case report form(s)
CRO	Contract (or clinical) research organization
CTX	C-type collagen sequence
CYP3A4	Cytochrome P450 3A4
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DXA	Dual energy x-ray absorptiometry
E2	Estradiol
EC	Ethics Committee

E/C/F	Elvitegravir/cobicistat/emtricitabine
eGFR	Estimated glomerular filtration rate
EFV	Efavienz
EKG / ECG	Electrocardiogram
ETV	Entecavir
EU	European Union
EVG	Elvitegravir
FAS	Full analysis set
FDA	(United States) Food and Drug Administration
$FEPO_4$	Fractional excretion of Phosphate
FRAX®	Fracture Risk Assessment Tool
FSH	Follicle stimulating hormone
FTC	Emtricitabine
GCP	Good Clinical Practice (Guidelines)
GFR	Glomerular filtration rate
GSI	Gilead Sciences, Inc.
GGT	Gamma glutamyl transferase
Hb	Hemoglobin
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HDPE	High-density polyethylene
hERG	Human ether-à-go-go-Related Gene
HIV	Human Immunodeficiency Virus
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
ITT	Intent-to-treat (analysis or subset)
IRB	Institutional review board
IV	Intravenous
IVRS	Interactive voice response system

IWRS	Interactive web response system
IUD	Intrauterine device
LdT	Telbivudine
LAM	Lamivudine
LLN	Lower limit of the normal range
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mmHg	Millimeters mercury
NK	Natural killer cells
NOEL	No observed adverse effect level
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Osteocalcin
OCT	Optical coherence tomography
OL	Open-label
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic
P-gp	P-glycoprotein
P1NP	Procollagen type 1 amino-terminal propeptide
pol	Polymerase
PK	Pharmacokinetic
PXR	Pregnane X receptor
PT	Preferred Term
PT/INR	Prothrombin time/ International normalized ratio
PVE	Pharmacovigilance and Epidemiology
QD	Once daily (use only in tables)
RNA	Ribonucleic acid
RPV	Rilpivirine
RT	Reverse transcriptase
SA	Single agent
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sCr	Serum creatinine
SD	Standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
STR	Single tablet regimen
SUSAR	Suspected Unexpected Serious Adverse Reaction

TAF	tenofovir alafenamide
TAF Fumarate	tenofovir alafenamide fumarate, GS-7340-03
TDF	tenofovir disoproxil fumarate
TFFU	Treatment Free Follow-Up
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TLOVR	Time to loss of virologic response
T_{max}	The time (observed time point) of C_{max}
$t_{½}$	An estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_3	Triiodothyronine
TSH	Thyroid stimulating hormone
UACR	Urine albumin-to-creatinine ratio
UGT1A1	Uridine glucuronosyltransferase 1 family, polypeptide A1
ULN	Upper limit of the normal range
UPCR	Urine protein-to-creatinine ratio
US	United States
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Chronic hepatitis B (CHB) is a major public health care issue worldwide and one of the principal causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The hepatitis B virus (HBV) is easily transmissible through perinatal, percutaneous, and sexual exposure {Lok 2009}. Following acute HBV infection, 5% to 10% of adults and up to 90% of children fail to produce an immune response adequate to clear the infection; these individuals become chronic carriers of the virus {Zuckerman 1996}. Individuals who develop CHB are at substantial risk of cirrhosis, hepatic decompensation, and HCC, which will afflict 15% to 40% of subjects with CHB in the absence of effective treatment {World Health Organization (WHO) 2015a, Wright 2006}. Liver cancer is the third leading cause of cancer deaths globally, with the highest burden of disease found in regions where HBV is endemic {Global Burden of Disease Cancer Collaboration 2015}. Recent reports estimated that 250 to 350 million individuals were living with HBV (i.e., are hepatitis B surface antigen [HBsAg] positive) in 2010, representing a worldwide prevalence of 3.6%, with considerable geographic variability {Schweitzer 2015, World Health Organization (WHO) 2015b}. For example, HBV prevalence rates of 0.01%, 0.76%, 4.0%, 5.5%, and 22.4% have been reported for the United Kingdom, Canada, Turkey, China, and South Sudan, respectively. In 2013, an estimated 686,000 deaths were due to HBV infection, placing it among the top 20 causes of mortality worldwide {G. B. D. Mortality Causes of Death Collaborators 2015, Ott 2012}. Worldwide universal vaccination remains the goal for eliminating HBV infection and its complications, yet despite the availability of HBV vaccine programs in many countries, new HBV infections are still common even in areas of low prevalence. The World Health Organization estimates that each year there are over 4 million acute clinical cases of HBV infection globally {World Health Organization (WHO) 2015b}. In the United States (US), approximately 20,000 people become acutely infected each year according to an estimate from the Centers for Disease Control and Prevention {Centers for Disease Control (CDC) 2013}.

The natural history of chronic hepatitis B virus infection and disease is complex and highly variable. Following acute hepatitis B infection, up to 90% of newborns who are vertically infected, and 25-50% of children who acquire HBV within the first 6 years of life, will become chronic carriers of the virus when the immune system is thought to be immature, compared to immunocompetent individuals who become infected during adulthood (< 1%) {Fattovich 2008, Sarin 2015}. CHB has traditionally been characterized by four distinct phases of variable duration that reflect the dynamics of viral replication and the evolving host immune response {Fattovich 2008, Sokal 2013}. Importantly, not all subjects will experience all phases of infection {Terrault 2015}. In the first, or the immune tolerant phase, individuals have high plasma levels of HBV DNA, detectable hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), with normal or slightly elevated serum alanine transaminase (ALT) levels reflective of minimal inflammation and fibrosis. This phase typically extends into late childhood or adolescence, and is followed by an HBeAg-positive, immune-active phase wherein ALT levels are persistently elevated along with fluctuating levels of HBV DNA, reflective of

moderate to severe inflammation or fibrosis. This phase may be followed by loss of HBeAg with seroconversion to anti-HBe. In the inactive CHB phase, subjects have undetectable or low levels of HBV DNA (< 2000 IU/mL), the presence of anti-HBe antibody, and normal or minimal elevation in serum ALT, which reflects minimal inflammation but with variable fibrosis. This third phase can evolve in a subgroup of individuals to an HBeAg-negative, immune reactivation phase, in which ALT levels and HBV DNA levels are increased. Subjects develop HBeAg-negative CHB as a result of variants that develop in the precore or core promoter region of the virus {Sarin 2015}. HBeAg-negative CHB affects about 10% of pediatric subjects {Sokal 2013}. The goal of anti-HBV therapy, in children as in adults, is to improve long-term survival and quality of life by reducing disease progression to cirrhosis, decompensated liver disease, and HCC {Sarin 2015, Sokal 2013}. As seroclearance of HBsAg is a rare spontaneous occurrence in children with CHB, durable anti-HBe seroconversion in HBeAg-positive subjects is considered a good endpoint, associated with improved prognosis, including a reduced risk of HCC. However, in many subjects who discontinue treatment following anti-HBe seroconversion, disease relapse with increased levels of viremia can occur {Sarin 2015}. As in adults, reduction of viremia to levels below assay detection can lead to reduced inflammation and slowing or reversal of fibrosis {Marcellin 2013, Sokal 2013}.

Currently, there are 2 approved options for treatment of CHB: injectable interferons and oral antiviral (OAV) agents. Of these, treatment with OAV agents has been more successful in achieving and maintaining a high degree of viral suppression in subjects with CHB. The development of nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) was a major breakthrough for the treatment of CHB, providing effective suppression of viral replication and reducing the risk of long-term complications {Marcellin 2013, World Health Organization (WHO) 2015a}. However, several N[t]RTIs possess a low barrier for viral resistance development, including lamivudine (LAM), telbivudine, (TBV) and adefovir dipivoxil (ADV) {European Association for the Study of the Liver (EASL) 2012, Liaw 2012}. Additionally, while development of resistance to entecavir (ETV) is low in treatment-naive subjects, the cumulative probability of ETV resistance increases substantially with long-term use in subjects, particularly in subjects who are refractory to lamivudine, and those with lamivudine resistance (up to 57% through 6 years of treatment) {Tenney 2009}. In contrast, resistance to tenofovir disoproxil fumarate (TDF; Viread®) has not been documented through 6 years of use {Kitrinos 2014}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits reverse transcription in HIV-1 and HBV. TDF, an oral prodrug of TFV, was first approved for the treatment of HIV infection in 2001 to be given in combination with other antiretroviral (ARV) agents and was approved for treatment of CHB as monotherapy in 2008. TDF is currently approved in over 165 countries, including the US, Canada, Europe, Japan, Taiwan, South Korea, and China, with more than 3,393,649 patient-years of use worldwide for both HIV and HBV infections since first marketing approval. TDF is a first-line treatment for CHB in all major treatment guidelines {European Association for the Study of the Liver (EASL) 2012, Liaw 2012, Lok 2009}. Although highly effective, use of TDF is associated with nephrotoxicity and bone-related toxicity in some subjects.

Tenofovir alafenamide (TAF) is a phosphonamide prodrug of TFV that is more stable in plasma than TDF, and provides higher intracellular levels of the active phosphorylated metabolite TFV-DP to target cells (eg, HBV-infected hepatocytes and HIV-infected lymphoid cells) with approximately 90% lower circulating levels of TFV relative to TDF at therapeutically active doses {Agarwal 2015, Babusis 2013, Murakami 2015, Ruane 2013}. The distinct metabolism of TAF offers the potential for an improved safety profile when compared with TDF. In support of this concept are recent results from a large dataset of 1733 HIV-infected, treatment naive subjects randomized to receive treatment with the fixed-dose combination [FDC] of the FDC of elvitegravir (E), cobicistat (C), emtricitabine (F), TAF [E/C/F/TAF; Genvoya®] or E/C/F/TDF [STB; Stribild®]). Renal and bone parameters were significantly less affected in subjects who received E/C/F/TAF compared with E/C/F/TDF {Sax 2015}. In adult subjects with CHB, a global Phase 3 program for TAF consisting of 2 prospective, randomized, active-controlled studies with 1 each in HBeAg-negative (Study GS-US-320-0108) and HBeAg-positive (Study GS-US-320-0110) subjects is currently ongoing as described below. A New Drug Application (NDA) for TAF 25 mg tablets was filed on 11-January, 2016 for the treatment of CHB in adults.

1.2. Tenofovir Alafenamide (TAF, GS-7340)

1.2.1. General Information

Tenofovir alafenamide (GS-7340, TAF, or L-Alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy] methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1) is a next generation oral prodrug of TFV, a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, TFV-DP, a competitive inhibitor of HIV-1 reverse transcriptase (RT) and HBV reverse transcriptase (HBV RT) that terminates the elongation of the viral DNA chain. In the development of TAF, three forms of the drug substance have been used in various studies: GS-7340, synonym for GS-7340 as the free base; GS-7340-02, synonym for TAF monofumarate (1:1); and GS-7340-03 as the hemifumarate (2:1). GS-7340-03, also known as TAF fumarate, which is being used in the Phase 3 studies GS-US-320-0108 and GS-US-320-0110, is considered comparable based on physical/chemical properties to GS-7340-02 that has been used in previous studies and a number of ongoing studies. GS-7340-03 was also used in the Phase 1b study GS-US-320-0101. GS-7340-03 and GS-7340-02 exist as the free base, TAF (GS-7340), in blood and biological fluids.

For further information on TAF (GS-7340), refer to the current investigator's brochure for TAF.

1.2.2. Preclinical Pharmacology and Toxicology

Virology

Following its release from the prodrug TAF, TFV is metabolized intracellularly to the active metabolite, TFV-DP, a competitive inhibitor of HBV polymerase/reverse transcriptase (pol/RT) and HIV-1 RT that terminates the elongation of the viral DNA chain during the process of HBV and retroviral replication.

Compared to TDF, TAF is relatively stable in plasma, but rapidly converts to TFV inside cells. The cellular enzymes responsible for conversion of TAF to TFV are cathepsin A (CatA), which is broadly expressed in cells, and carboxylesterase 1 (CES1), which is highly expressed in liver. In HBV target cells, primary human hepatocytes, TAF is primarily hydrolyzed by CES1 with CatA making a minor contribution {Murakami 2015}. In HIV-1 target cells, primary human lymphoid cells, CatA is the major enzyme hydrolyzing TAF to TFV. In vitro studies have shown no significant variation for conversion to TFV and antiviral activity of TAF within PBMCs and macrophages from multiple donors. The covalent anti-hepatitis C virus (HCV) protease inhibitors (PIs) telaprevir and boceprevir were identified as the only potent inhibitors of CatA mediated hydrolysis of TAF in a biochemical assay (PC-120-2001).

TAF is a potent inhibitor of HBV replication, exhibiting in vitro activity comparable to that of TDF with an EC_{50} value of 18 nM. Additionally, TAF is similarly active in vitro against wild-type genotype A-H HBV clinical isolates (PC-320-2003). TAF also exhibits potent anti-HIV activity in lymphoid T-cells, primary human PBMCs, and macrophages with EC_{50} values ranging from 3 to 14 nM. The in vitro activity of TAF against HIV-1 is 100- to 600-fold greater than TFV and 4- to 6-fold greater than TDF {Robbins 1998}. In MT-2 cells, TAF shows low cytotoxicity with a selectivity index of > 10,000. Based on data generated with the parent nucleotide TFV, TAF is active against a wide range of HIV-1 subtypes and also against HIV-2.

For further information on the virology of TAF, (GS-7340), refer to the current investigator's brochure for TAF.

Safety Pharmacology

The IC_{20} and the IC_{50} for the inhibitory effect of TAF fumarate on human ether-a-go-go-related gene (hERG) potassium current was estimated to be greater than 30 μM (PC-120-2005). TAF in the monofumarate form has been evaluated to determine potential functional effects on the central nervous system (R990188), renal system (R990186), cardiovascular (D2000006), and gastrointestinal systems (R990187). Single doses did not induce pharmacologic effects on the central nervous system of the rat (1000 mg/kg), the renal system of the rat (1000 mg/kg), or the cardiovascular system of the dog (100 mg/kg). TAF at 1000 mg/kg reduced distal transit and increased stomach weights starting 2 hours postdosing, with reversibility beginning by 6 hours after dosing. The no observed effect level (NOEL) for gastrointestinal motility was 100 mg/kg.

Nonclinical Pharmacokinetics

All nonclinical pharmacokinetic experiments were performed using TAF monofumarate (GS-7340-02), and all study data described reflect the dosage of the monofumarate. For reference, 100 mg of TAF monofumarate is equivalent to 80 mg of the GS-7340 free base (TAF).

Plasma pharmacokinetics of the intact prodrug, TAF, following oral administration of GS-7340-02 in dogs and monkeys demonstrated rapid absorption with peak plasma concentrations between 0.25 and 0.5 hours.

Peak TFV plasma concentrations occurred following TAF absorption, with TFV T_{max} values between 0.25 to 1.7 hours in rats, dogs, and monkeys. TFV plasma concentrations declined with a terminal half-life of 11.2 to 16.4 hours in rats (fasted), > 24 hours in dogs (fasted) and 8.1 to 2.5 hours in rhesus monkeys.

The tissue distribution and recovery of [^{14}C] radiolabeled GS-7340-02 was examined in beagle dogs. Radioactivity was detected in all tissues except brain, with the majority present in the contents of the gastrointestinal tract, liver, kidney, and large intestine. Tissue concentrations were the highest in kidney, PBMCs, liver, large intestine, and bile. Significant concentrations of TFV-related radioactive material were observed in lymph nodes from all 4 sites, suggesting that TAF may be selectively cleaved to tenofovir in the cells of the lymphoreticular system. The primary route of elimination of tenofovir is renal excretion of unchanged drug based on intravenous studies of TFV. Following oral administration of GS-7340-02, approximately 15% of a radiolabeled dose is recovered in dog urine in 24 hours. Tenofovir was the major species present in the urine (90%), with about 3.4% of TAF also present. Biliary excretion of tenofovir in dogs and fecal elimination of tenofovir in rats and dogs are negligible.

Tenofovir was the only species found in the intestinal contents and feces. In human systems, TAF is metabolized by hydrolytic cleavage and, to a lesser extent, by CYP3A4 catalyzed oxidation (AD-120-2004). As a result of the limited metabolism of TAF by CYP3A4 inhibition or induction of this enzyme should have little consequence on TAF exposure in vivo. TAF has limited potential to alter CYP enzyme activity through inhibition and does not inhibit UGT1A1 function. In addition, TAF is not an activator of either the aryl hydrocarbon receptor (AhR) or human pregnane-X-receptor (PXR). These features combined with the relatively low plasma exposures of TAF in humans suggest that the potential of TAF to cause or be affected by clinically relevant drug-drug interactions is very low.

Nonclinical Toxicology

Because of lack of exposure to the prodrug TAF in mice and rats and achievable TFV exposures being less than previously tested in studies with TDF, Gilead and regulatory agencies have agreed that neither carcinogenicity studies nor a peri/postnatal study with TAF were warranted as they would not add to the overall risk evaluation or risk management of TAF.

The oral toxicity of TAF was evaluated in mice, rats, dogs, and monkeys for treatment periods up to 9 months. Based on recommendations that renal karyomegaly is not a dose-limiting effect {Foran 1997} and observations in the rat that renal karyomegaly is not sufficient to induce renal toxicity or predict oncogenicity (M990205) (M990204), its toxicological significance is questionable and, therefore, it was not considered an adverse effect in determining the NOAEL.

The data from the 6-month rat study determined a NOAEL of 25 mg/kg/day; the 9-month dog study defined a NOAEL of 2 mg/kg/day, and the 28-day nonhuman primate study defined a NOAEL of ≥ 30 mg/kg/day. While no NOAEL was determined in the 13-week mouse study, the relevance of the nasal findings to humans is unclear.

TAF had no discernible electrocardiograph effect at the low dose of 2 mg/kg/day. There was some evidence at 6 and 18/12 mg/kg/day for an effect to slightly prolong PR intervals. Additionally, at Week 39, TAF appeared to reversibly reduce heart rate with an associated mild QT prolongation. At Week 39, significant decreases in serum tri-iodothyronine (T3) were noted for animals receiving 18/12 mg/kg/day when compared to controls, which may have been associated with the slight prolongation of PR intervals. After the 3-month recovery period, serum T3 values returned to levels similar to the control group animals at the end of the study.

TAF was not genotoxic in either in vitro or in vivo assays. TAF fumarate had no adverse effects on male or female fertility parameters in rats. There was no effect on fetal viability or fetal development in pregnant rats administered doses of TAF monofumarate up to 200 mg/kg/day or in pregnant rabbits administered TAF monofumarate up to 100 mg/kg/day the highest doses tested. In the rat, a minor (7.7%) decrease in mean fetal body weight compared to the control group was observed at 200 mg/kg/day, which was a maternally toxic dose. At the NOAEL for embryo-fetal development of 200 mg/kg/day in rats, AUC_{tau} values for TAF and TFV on Day 17 were 0.65 and 35.7 µg•h/kg, respectively. At the NOEL for embryo-fetal development of 100 mg/kg/day in rabbits, AUC_{tau} values for TAF and TFV on Day 20 were 10.7 and 23.5 µg•h/kg, respectively. The TFV exposures in both species were > 30-fold higher than the TFV AUC_{inf} after a 25-mg dose of TAF monofumarate in humans.

For further information on TAF, (GS-7340), refer to the current investigator's brochure for TAF.

1.2.3. Clinical Trials of Tenofovir Alafenamide (TAF, GS-7340)

As of December 2015, a total of 1286 subjects have received at least 1 dose of TAF 25 mg in the TAF clinical program, including 866 subjects in the TAF Phase 3 studies in subjects with CHB and 420 subjects in TAF single-agent Phase 1 studies. The TAF clinical development program for CHB includes 2 ongoing Phase 3 studies in hepatitis B e antigen (HBeAg)-negative and HBeAg-positive subjects with CHB, a Phase 1b antiviral activity and safety/tolerability study in subjects with CHB, as well as several Phase 1 safety, PK/pharmacodynamics (PD), and drug interaction studies in healthy subjects (including Chinese and Japanese subjects) and in subjects with impaired renal or hepatic function.

In some studies, TAF was administered as a single agent or as part of the F/TAF, FTC/RPV/TAF, or E/C/F/TAF FDC tablets.

TAF clinical studies are listed below:

- **GS-US-320-0101**, a Phase 1b study to evaluate the pharmacokinetics, safety, viral kinetics, and anti-HBV activity of TAF in treatment-naive adults with CHB (completed) {Agarwal 2015}

- **GS-US-320-1228**, a Phase 1 study to evaluate the pharmacokinetics, safety, and tolerability of TAF in healthy Japanese and non-Japanese subjects (completed)

- **GS-US-320-1229**, a Phase 1 study to evaluate the pharmacokinetics of a single dose and repeat doses of TAF 25 mg in healthy Chinese subjects (completed; data analysis is completed)

- **GS-US-320-1382**, a Phase 1 study to evaluate the effect of food on a single dose of TAF 25 mg in healthy subjects (completed)

- **GS-US-320-1615**, a Phase 1 study to evaluate the pharmacokinetics of a single dose of TAF 25 mg in subjects with severe hepatic impairment and subjects with normal liver function (completed)

- **GS-US-320-0108**, a Phase 3 study to evaluate the safety and efficacy of TAF 25 mg once daily versus TDF 300 mg once daily for the treatment of HBeAg-negative subjects with CHB (ongoing)

- **GS-US-320-0110**, a Phase 3 study to evaluate the safety and efficacy of TAF 25 mg once daily versus TDF 300 mg once daily for the treatment of HBeAg-positive subjects with CHB (ongoing)

- **GS-US-120-0108**, a Phase 1, open-label, parallel-design study to evaluate the pharmacokinetics of TAF in subjects with severe renal impairment (completed)

- **GS-US-120-0109**, a Phase 1 mass balance study to evaluate the pharmacokinetics, metabolism and excretion of TAF in healthy subjects (completed)

- **GS-US-120-0114**, a Phase 1 study to evaluate the pharmacokinetics of TAF in subjects with normal, mild, and moderately impaired hepatic function (completed)

- **GS-US-120-1538**, a Phase 1 pharmacokinetic study that evaluated the drug interaction potential between TAF and MDZ (oral and intravenous) in healthy subjects (completed)

- **GS-US-120-1554**, a Phase 1 pharmacokinetic study that evaluated the drug interaction potential between TAF and RPV in healthy subjects (completed)

- **GS-US-311-1386**, a Phase 1 study that evaluated the effect of food on the PK of TAF and FTC when administered as an F/TAF fixed-dose combination tablet in healthy subjects (completed)

- **GS-US-311-1387**, a Phase 1 study that evaluated the drug-drug interaction (DDI) potential between CBZ and TAF administered as F/TAF in healthy subjects (completed)

- **GS-US-311-1790**, a Phase 1 study that evaluated the DDI potential between F/TAF or GS-9883 and norgestimate/ethinyl estradiol in healthy female subjects (completed)

- **GS-US-320-4018**, a Phase 3, randomized (1:1), double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of TAF 25 mg every day (QD) in virologically suppressed subjects who switch from TDF to TAF compared to continued TDF treatment (ongoing)

- **GS-US-320-4035**, a Phase 2, open label, multi-center, single-arm study to evaluate the safety, tolerability, and efficacy of switching to TAF 25 mg QD in virologically suppressed subjects with CHB and renal impairment (moderate or severe renal impairment, or those with end-stage renal disease (ESRD) maintained on hemodialysis), and/or hepatic impairment (Child-Pugh-Turcotte Class B and C) (ongoing)

- **GS-US-320-1092**, A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection (ongoing)

- **GS-US-320-1196**, A Phase 1, Single-Dose, Cross-Over Study Evaluating the Relative Bioavailability of a Pediatric Oral Granule Formulation of Tenofovir Alafenamide in Healthy Adults (planned)

Please refer to the latest version of the investigator's brochure for additional information.

An overview of the 2 Phase 3 studies evaluating the efficacy and safety of TAF in Marketing Applications is provided in Table 1-1. The Phase 3 studies are described below as follows:

- **GS-US-320-0108:** This ongoing Phase 3, randomized, double-blind, noninferiority, international, multicenter study is comparing the efficacy, safety, and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for 48 weeks for the treatment of CHB infection in treatment-naive and treatment-experienced HBeAg-negative subjects.

- **GS-US-320-0110:** This ongoing Phase 3, randomized, double-blind, noninferiority, international, multicenter study is comparing the efficacy, safety, and tolerability of TAF 25 mg once daily versus TDF 300 mg once daily for 48 weeks for the treatment of CHB infection in treatment-naive and treatment-experienced HBeAg-positive subjects.

In both of these similarly designed noninferiority studies, subjects were randomized in a 2:1 ratio to receive either TAF 25 mg or TDF 300 mg once daily for 96 weeks. Randomization was stratified by plasma HBV DNA level (< 7, ≥ 7 to < 8, and ≥ 8 $\log_{10}$ IU/mL for Study GS-US-320-0108; < 8 and ≥ 8 $\log_{10}$ IU/mL for Study GS-US-320-0110) and OAV treatment status (treatment naive vs treatment experienced) at screening. In both studies, all subjects completing 96 weeks of double-blind therapy are eligible to continue open-label treatment with TAF 25 mg for an additional 48 weeks. Both protocols were amended in February 2016 (Amendment 3 of GS-US-320-0108 and GS-US-320-0110) to extend the double-blind period to 144 weeks (3 years) and the open-label phase from Week 144 to Week 384 (8 year total study period).

Table 1-1. Clinical Studies to Support Efficacy for the TAF Marketing Applications

Study	Study Design	Treatment Regimen (Number of Subjects[a])	Data Presented
GS-US-320-0108	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF vs TDF in HBeAg-negative subjects with CHB	TAF 25 mg once daily (N = 285) TDF 300 mg once daily (N = 140)	Week 48 efficacy, PK, and safety
GS-US-320-0110	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of TAF vs TDF in HBeAg-positive subjects with CHB	TAF 25 mg once daily (N = 581) TDF 300 mg once daily (N = 292)	Week 48 efficacy, PK, and safety

Demographic and disease characteristics were generally similar between the TAF and TDF groups in both studies and are representative of patient population of HBeAg-negative subjects in Study GS-US-320-0108 and HBeAg-positive subjects in Study GS-US-320-0110. In both studies the majority of subjects were male (> 60%) and Asian (> 70%). As would be expected based on the 2 distinct study populations, subjects in Study GS-US-320-0108 were older (median age: 47 years; range: 19-80 years) than subjects in Study GS-US-320-0110 (median age: 36 years; range: 18-69 years). Differences in baseline characteristics between the 2 studies included HBV DNA levels (median levels were 5.7 and 7.9 $\log_{10}$ IU/mL for GS-US-320-0108 and GS-US-320-0110, respectively), serum ALT levels (median values were 67 and 85 U/L for GS-US-320-0108 and GS-US-320-0110, respectively), and number of years positive for HBV (6.0 and 4.0 years [median values] for GS-US-320-0108 and GS-US-320-0110, respectively). The distribution of HBV genotypes was similar between treatment groups in both studies with the most common genotypes being C (46.1%), D (24.3%), and B (20.4%).

Efficacy of TAF in Subjects with CHB

Primary Endpoint Analysis

For both studies, the primary efficacy endpoint was the proportion of subjects with plasma HBV DNA < 29 IU/mL at Week 48. Table 1-2 presents HBV DNA outcomes for Studies GS-US-320-0108 and GS-US-320-0110 for subjects at Week 48. In both studies, similar rates of HBV DNA suppression were achieved in the 2 treatment groups when assessed using the M = F method at Week 48 for the Full Analysis Set (FAS). The percentages of subjects with HBV DNA levels < 29 IU/mL at Week 48 were as follows:

- **Study GS-US-320-0108:** TAF 94.0%, TDF 92.9%; difference in proportions (baseline stratum-adjusted): 1.8%, 95% CI: −3.6% to 7.2%
- **Study GS-US-320-0110:** TAF 63.9%, TDF 66.8%; difference in proportions (baseline stratum-adjusted): −3.6%, 95% CI: −9.8% to 2.6%

In both studies, because the lower bound of the 2-sided 95% CI of the difference (TAF − TDF) in the response rate was greater than the prespecified −10% margin, the TAF group met the primary endpoint of noninferiority to the TDF group.

Table 1-2. GS-US-320-0108 and GS-US-320-0110: HBV DNA Outcome at Week 48 Using HBV DNA of < 29 IU/mL, Missing = Failure (Full Analysis Set)

	GS-US-320-0108		GS-US-320-0110	
	TAF 25 mg (N = 285)	**TDF 300 mg (N = 140)**	**TAF 25 mg (N = 581)**	**TDF 300 mg (N = 292)**
HBV DNA < 29 IU/mL	268 (94.0%)	130 (92.9%)	371 (63.9%)	195 (66.8%)
P-value[a]	0.47		0.25	
Difference in Proportions (95% CI)[b]	1.8% (−3.6% to 7.2%)		−3.6% (−9.8% to 2.6%)	
HBV DNA ≥ 29 IU/mL	7 (2.5%)	4 (2.9%)	183 (31.5%)	88 (30.1%)
No Virologic Data at Week 48	10 (3.5%)	6 (4.3%)	27 (4.6%)	9 (3.1%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	1 (0.2%)	0
Discontinued Study Drug Due to AE/Death	3 (1.1%)	1 (0.7%)	6 (1.0%)	3 (1.0%)
Discontinued Study Drug Due to Other Reasons[c]	6 (2.1%)	4 (2.9%)	19 (3.3%)	6 (2.1%)
Missing Data During Window but on Study Drug	1 (0.4%)	1 (0.7%)	1 (0.2%)	0

Biochemical Analyses

Table 1-3 presents the proportion of subjects with ALT normalization at Week 48 for both studies (GS-US-320-0108) and (GS-US-320-0110) when determined by central laboratory criteria and by AASLD criteria (upper limit of normal range: ≤ 30 U/L for males and ≤ 19 U/L for females {Lok 2009, Terrault 2015}), respectively.

For Study GS-US-320-0108, the percentage of subjects with normalized ALT (i.e., ALT > ULN at baseline but within the normal range at Week 48) using the central laboratory criteria was numerically higher for the TAF group compared with the TDF group for all time points from Weeks 4 through 48. When assessed at Week 48, rates of ALT normalization were not significantly different between the 2 treatment groups by the M = F method for the FAS. Using the AASLD criteria, the percentage of subjects with normalized ALT was significantly higher in the TAF group than in the TDF group at all time points from Week 8 onward using the M = F method.

For Study GS-US-320-0110, the percentage of subjects with normalized ALT using the central laboratory criteria was numerically higher for the TAF group compared with the TDF group for all time points from Weeks 8 through 48. When assessed at Week 48, rates of normalization were not significantly different between the 2 treatment groups by the M = F method for the FAS. Using the AASLD criteria, the percentage of subjects with normalized ALT was significantly higher in the TAF group than in the TDF group at all time points from Weeks 8 through 48 using the M = F method.

Overall, the percentage of subjects with normalized ALT at Week 48 was higher in Study GS-US-320-0108 compared with Study GS-US-320-0110 using the central laboratory criteria and similar across the 2 studies using the AASLD criteria.

Table 1-3. GS-US-320-0108 and GS-US-320-0110: Proportion of Subjects with ALT Normalization at Week 48, Missing = Failure (Full Analysis Set with Baseline ALT > ULN)

	GS-US-320-0108		GS-US-320-0110	
Normalized ALT	**TAF 25 mg**	**TDF 300 mg**	**TAF 25 mg**	**TDF 300 mg**
Central Laboratory[a]	**(N = 236)**	**(N = 121)**	**(N = 537)**	**(N = 268)**
Week 48	196/236 (83.1%)	91/121 (75.2%)	384/537 (71.5%)	179/268 (66.8%)
Proportion Difference (95% CI)	8.0% (−1.3% to 17.2%)		4.6% (−2.3% to 11.4%)	
p-value	0.076		0.18	
AASLD[b]	**(N = 276)**	**(N = 138)**	**(N = 572)**	**(N = 290)**
Week 48	137/276 (49.6%)	44/138 (31.9%)	257/572 (44.9%)	105/290 (36.2%)
Proportion Difference (95% CI)	17.9% (8.0% to 27.7%)		8.7% (1.8% to 15.6%)	
p-value	< 0.001		0.014	

a Central laboratory ULN for ALT are as follows: ≤ 43 U/L for males aged 18 to < 69 years and ≤ 35 U/L for males ≥ 69 years; ≤ 34 U/L for females 18 to < 69 years and ≤ 32 U/L for females ≥ 69 years.
b AASLD ULN for ALT criteria are as follows: ≤ 30 U/L for males and ≤ 19 U/L for females.
P-value was from the Cochran-Mantel-Haenszel tests stratified by baseline HBV DNA categories and oral antiviral treatment status strata
Difference in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.
Source: GS-US-320-0108 Week 48 CSR, Section 15.1, Tables 23.1.1 and 23.2.1; GS-US-320-0110 Week 48 CSR, Section 15.1, Tables 23.1.1 and 23.2.1

Serological Analyses

In Study GS-US-320-0108, no subject in either treatment group experienced HBsAg loss by Week 48. In Study GS-US-320-0110, 4 subjects (0.7%) in the TAF group and 1 subject (0.3%) in the TDF group experienced HBsAg loss at Week 48. Three of the 4 subjects in the TAF group and none in the TDF group also experienced HBsAg seroconversion at Week 48.

In Study GS-US-320-0110, the proportion of subjects with HBeAg loss or seroconversion to anti-HBe at Week 48 was also evaluated; these data are presented on Table 1-4. A total of 78 (13.8%) and 34 (11.9%) subjects in the TAF and TDF groups, respectively, had HBeAg loss at Week 48. A total of 58 (10.3%) and 23 (8.1%) subjects in the TAF and TDF groups, respectively, experienced HBeAg seroconversion at Week 48.

Table 1-4. GS-US-320-0110: Proportion of Subjects with HBeAg Loss or Seroconversion at Week 48, Missing = Failure (Serologically Evaluable Full Analysis Set)

	GS-US-320-0110			
			TAF 25 mg vs TDF 300 mg	
	TAF 25 mg (N = 565)	TDF 300 mg (N = 285)	p-value	Prop Diff (95% CI)
HBeAg Loss, n (%)	78/565 (13.8%)	34/285 (11.9%)	0.47	1.8% (−3.0% to 6.5%)
HBeAg Seroconversion, n (%)	58/565 (10.3%)	23/285 (8.1%)	0.32	2.1% (−2.0% to 6.3%)

P-values were from the Cochran-Mantel-Haenszel test stratified by baseline HBV DNA categories and oral antiviral treatment status. Differences in the proportion between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and oral antiviral treatment status strata.
Serologically Evaluable Full Analysis Set for HBeAg loss/seroconversion included subjects who were HBeAg positive and HBeAb negative/missing at baseline. HBeAg loss was defined as changes from HBeAg-positive at baseline to HBeAg-negative at a post-baseline visit with baseline anti-HBe negative/missing. HBeAg seroconversion was defined as HBeAg loss and anti-HBe change from negative/missing at baseline to positive at a post-baseline visit.
Source: GS-US-320-0110 Week 48 CSR, Section 15.1, Table 19.1

Virologic Resistance Analysis

In an integrated analysis of Studies GS-US-320-0108 and GS-US-320-0110, 24 subjects (2.8%) in the TAF group and 14 subjects (3.2%) in the TDF group qualified for population-based sequence analysis after up to 48 weeks of treatment. Among the 24 subjects in the TAF group who qualified for population-based sequence analysis, 15 had no changes detected in the pol/RT sequence from baseline, 4 were unable to be sequenced, and 5 had polymorphic site substitutions. Among the 14 subjects in the TDF treatment group who qualified for population-based sequence analysis, 6 had no changes detected in the pol/RT sequence from baseline, 4 were unable to be sequenced, 2 had polymorphic site substitutions, and 2 had a conserved site substitution. Overall, no HBV pol/RT amino acid substitutions associated with resistance to TFV were detected through 48 weeks of the study in either treatment group.

Safety of TAF in CHB Subjects

The principal sources of safety data for TAF are presented above in Table 1-1 and consist of 2 Phase 3 studies in subjects with CHB, Study GS-US-320-0108 and GS-US-320-0110. Subjects included in the Safety Analysis Set received at least 1 dose of study drug.

Overall Extent of Exposure

Of the 2387 subjects screened in Studies GS-US-320-0108 and GS-US-320-0110 combined, 1301 were randomized (TAF 867 subjects; TDF 434 subjects), and 1298 received at least 1 dose of study drugs (TAF 866 subjects; TDF 432 subjects); 3 subjects (TAF 1 subject; TDF 2 subjects) did not receive study drug due to withdrawal of consent. As of the Week 48 data cutoff date for each Phase 3 study, a total of 1208 subjects (TAF 93.1%, 806 subjects;

TDF 93.1%, 402 subjects) were continuing double-blind study drugs, and 27 subjects (TAF 2.1%, 18 subjects; TDF 2.1%, 9 subjects) had entered the open-label phase as of the Week 48 data cutoff date. Of the 1298 subjects randomized and treated, 63 subjects (4.9%) discontinued blinded study drugs (TAF 4.8%, 42 subjects; TDF 4.9%, 21 subjects), and 61 subjects (TAF 40 subjects; TDF 21 subjects) discontinued from the study prior to the Week 48 data cutoff date. Similar rates of discontinuation and reasons for treatment discontinuation were observed for TAF compared with TDF. The most common reasons for premature discontinuation of blinded study treatment were withdrew consent (TAF 1.6%, 14 subjects; TDF 1.6%, 7 subjects); adverse event (AE; TAF 1.0%, 9 subjects; TDF 1.2%, 5 subjects); and lost to follow-up (TAF 0.7%, 6 subjects; TDF 0.7%, 3 subjects). The most common reasons for discontinuation from the study were: subjects withdrew consent (TAF 2.0%, 17 subjects; TDF 2.1%, 9 subjects), lost to follow-up (TAF 0.8%, 7 subjects; TDF 0.7%, 3 subjects), and AEs (TAF 0.3%, 3 subjects; TDF 0.9%, 4 subjects).

Table 1-5 summarizes the duration of exposure to blinded study drug in the TAF Phase 3 Safety Population. Median (first quartile [Q1], third quartile [Q3]) exposures were nearly identical between the 2 treatment groups (TAF 56.1 [48.1, 64.4] weeks; TDF 56.1 [48.1, 64.7] weeks. More than half of the subjects in each treatment group had received blinded study drug for ≥ 56 weeks at the time of the Week 48 data cutoff date for each Phase 3 study (TAF 60.5 %, 524 subjects; TDF 62.0 %, 268 subjects). There was no statistically significant difference between groups in the overall Kaplan-Meier estimate of time to premature discontinuation of blinded study drug.

Table 1-5. GS-US-320-0108 and GS-US-320-0110: Subjects Exposed to Study Drug for the TAF Phase 3 Safety Population (Safety Analysis Set)

Duration of Exposure to Study Regimen (Weeks)	GS-US-320-0108 and GS-US-320-0110	
	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
N	866	432
Mean (SD)	58.9 (14.71)	59.0 (15.58)
Median	56.1	56.1
Q1, Q3	48.1, 64.4	48.1, 64.7
Min, Max	0.1, 96.3	0.1, 96.3
Total Exposure to Study Drug n(%)		
≥ 4 Weeks [28 days]	860 (99.3%)	426 (98.6%)
≥ 8 weeks [56 days]	858 (99.1%)	426 (98.6%)
≥ 12weeks [84 days]	854 (98.6%)	423 (97.9%)
≥ 16 Weeks [112 days]	851 (98.3%)	422 (97.7%)
≥ 20 Weeks [140 days]	851 (98.3%)	422 (97.7%)
≥ 24 Weeks [168 days]	851 (98.3%)	419 (97.0%)
≥ 28 Weeks [196 days]	849 (98.0%)	418 (96.8%)
≥ 32 Weeks [224 days]	843 (97.3%)	418 (96.8%)
≥ 36 Weeks [252 days]	838 (96.8%)	418 (96.8%)
≥ 40 Weeks [280 days]	835 (96.4%)	418 (96.8%)
≥ 44 Weeks [308 days]	832 (96.1%)	418 (96.8%)
≥ 48 Weeks [336 days]	669 (77.3%)	346 (80.1%)
CCI		

Duration of exposure to blinded study drug was the number of weeks between the first dose and the last dose of blinded study drug. If the last dose date of blinded study drug is missing for subjects prematurely discontinued blinded study drug, or for subjects still on blinded study drug, the latest of nonmissing blinded study drug start and end dates or clinic and laboratory visit dates (excluding open-label and treatment-free follow-up visits) was used to impute the last dose date of blinded study drug.
Source: TAF Week 48 ISS, Table 4

Adverse Events for the TAF Phase 3 Safety Population (Week 48)

Summary of Adverse Events

Table 1-6 presents an overall summary of AEs by treatment group for the TAF Phase 3 Safety Population. Similar percentages of subjects in each treatment group had experienced at least 1 AE (TAF 70.2 %, 608 subjects; TDF 67.4%, 291 subjects) and had experienced at least 1 Grade 3 or 4 AE (TAF 4.5 %, 39 subjects; TDF 3.9 %, 17 subjects). In addition, 57 subjects (TAF 4.2%, 36 subjects; TDF 4.9 %, 21 subjects) had at least 1 SAE, with no subjects experiencing a treatment-related SAE. A similar percentage of subjects in each treatment group experienced an AE leading to discontinuation of study drugs (TAF 1.0%, 9 subjects; TDF 1.2%, 5 subjects). No deaths occurred in any subject on treatment. There were 2 deaths which occurred after treatment was discontinued and were considered non-treatment emergent (1 subject in each treatment group).

Table 1-6. GS-US-320-0108 and GS-US-320-0110: Overall Summary of Adverse Events in the TAF Phase 3 Safety Population (Safety Analysis Set)

Adverse Events	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Subjects Experiencing Any AE	608 (70.2%)	291 (67.4%)
Subjects Experiencing Any Grade 2, 3, or 4 AE	221 (25.5%)	120 (27.8%)
Subjects Experiencing Any Grade 3 or 4 AE	39 (4.5%)	17 (3.9%)
Subjects Experiencing Any Study Drug-Related AE	123 (14.2%)	68 (15.7%)
Subjects Experiencing Any Grade 2, 3, or 4 Study Drug-Related AE	33 (3.8%)	21 (4.9%)
Subjects Experiencing Any Grade 3 or 4 Study Drug-Related AE	6 (0.7%)	2 (0.5%)
Subjects Experiencing Any SAE	36 (4.2%)	21 (4.9%)
Subjects Experiencing Any Study Drug-Related SAE	0	0
Subjects Experiencing Any AE Leading to Premature Study Drug Discontinuation	9 (1.0%)	5 (1.2%)
Subjects Experiencing Any AE Leading to Dose Modification or Study Drug Interruption	17 (2.0%)	7 (1.6%)
Death[a]	0	0

a Treatment-emergent death refers to the death occurred between the first dose date and the last dose date (inclusive). Adverse events were mapped according to MedDRA Version 18.

Treatment-emergent AEs was defined as follows:

1) Any AEs with onset date of on or after the study drug start date and no later than the study drug stop date for those who discontinued study drug permanently, or
2) Any AE with an onset date on or after the study drugs start date for those who had not discontinued study drug permanently, or
3) Any AEs leading to study drug discontinuation

Source: TAF Week 48 ISS, Table 6

Common Adverse Events

Table 1-7 presents AEs reported for ≥ 5% of subjects for any treatment group by system organ class (SOC) and preferred term (PT) in the TAF Phase 3 Safety Population. The rate and types of AEs were similar in the 2 treatment groups. Overall, the 3 most frequently reported AEs by treatment group were as follows:

- **TAF group** — upper respiratory tract infection (9.9%, 86 subjects), nasopharyngitis (9.9%, 86 subjects), and headache (9.5%, 82 subjects)
- **TDF group** — headache (8.3%, 36 subjects), upper respiratory tract infection (7.4%, 32 subjects), and nasopharyngitis (7.2%, 31 subjects)

Table 1-7. GS-US-320-0108 and GS-US-320-0110: Adverse Events Reported for ≥ 5% of Subjects in Either Treatment Group in the TAF Phase 3 Safety Population (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b,c]	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Number of Subjects Experiencing Any Adverse Event	608 (70.2%)	291 (67.4%)
Gastrointestinal disorders	227 (26.2%)	108 (25.0%)
Nausea	43 (5.0%)	22 (5.1%)
General disorders and administration site conditions	125 (14.4%)	62 (14.4%)
Fatigue	49 (5.7%)	23 (5.3%)
Infections and infestations	259 (29.9%)	121 (28.0%)
Upper respiratory tract infection	86 (9.9%)	32 (7.4%)
Nasopharyngitis	86 (9.9%)	31 (7.2%)
Nervous system disorders	149 (17.2%)	60 (13.9%)
Headache	82 (9.5%)	36 (8.3%)
Respiratory, thoracic and mediastinal disorders	106 (12.2%)	44 (10.2%)
Cough	55 (6.4%)	27 (6.3%)

a Adverse events were mapped according to MedDRA Version 18.
b SOC were presented alphabetically, and PT was presented by decreasing order of the total frequencies.
c Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: TAF Week 48 ISS, Table 7

Adverse Events by Severity

The majority of AEs reported in the TAF Phase 3 Safety Population were Grade 1 or 2. A similar percentage of subjects in each treatment group experienced at least 1 Grade 3 AE (TAF 4.5%, 39 subjects; TDF 3.9%, 17 subjects). No subjects in either group had a Grade 4 AE. The only Grade 3 AE that occurred in more than 2 subjects in either treatment group were increased ALT (TAF 0.6%, 5 subjects; TDF 0.7%, 3 subjects) and hepatocellular carcinoma (HCC) (TAF 0 subjects; TDF 0.7%, 3 subjects). Four Grade 3 ALT increases (TAF 3 subjects; TDF 1 subject) were assessed as related to study drug.

Serious Adverse Events

Table 1-8 presents SAEs reported for > 1 subjects for any treatment group in the TAF Phase 3 Safety Population. A similar percentage of subjects experienced SAEs in each treatment group (TAF 4.2%, 36 subjects; TDF 4.9%, 21 subjects). None of the SAEs were considered related to study drugs by the investigators. Hepatocellular carcinoma was reported for 6 subjects (TAF 0.1%, 1 of 866 subjects; TDF 1.2%, 5 of 432 subjects). Other SAEs reported in > 1 subject in either treatment group were cellulitis, hand fracture, dizziness, and calculus ureteric.

Table 1-8. GS-US-320-0108 and GS-US-320-0110: Serious Adverse Events by Treatment Regimen in > 1 Subject in the TAF Phase 3 Safety Population (Safety Analysis Set)

Preferred Term[a,b]	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Number of Subjects (%) Experiencing Any SAE	36 (4.2%)	21 (4.9%)
Hepatocellular carcinoma	1 (0.1%)	5 (1.2%)
Cellulitis	0	3 (0.7%)
Hand fracture	2 (0.2%)	0
Dizziness	2 (0.2%)	0
Calculus ureteric	2 (0.2%)	0

a Adverse events were mapped according to MedDRA Version 18.
b Multiple AEs were counted only once per subject for each SOC and PT, respectively.
Source: TAF Week 48 ISS, Table 14

Summary of Bone Safety

Bone safety was assessed in the TAF Phase 3 Safety Population due to decreases in bone mineral density (BMD) and mineralization defects that have been seen in subjects treated with TDF.

Summary of Fractures

In the TAF Phase 3 Safety Population, the incidence of fracture events was uncommon (TAF 0.7%, 6 of 866 subjects; TDF 0.2%, 1 of 432 subjects; p = 0.44).
Six of the 7 reported fractures were associated with trauma and 1 subject, in the TAF group, had a spinal compression fracture identified incidentally on a computed tomography (CT) scan. In the TAF group, 4 fractures were reported as SAEs (hand fracture [3 subjects] and 1 spinal compression fracture). In the TDF group, 1 fracture (lower limb fracture) was reported as an SAE. Of the 7 subjects who had fractures, 4 subjects in the TAF group (tibia fracture, spinal compression identified incidentally, hand fracture [2 subjects]) had normal hip and spine BMD T-scores at all timepoints, 2 subjects in the TAF group (hand fracture and traumatic spinal compression fracture) had hip and/or spine baseline BMD T-scores consistent with osteoporosis at baseline, 1 subject in the TDF group (lower limb fracture) had normal hip and spine BMD at baseline which worsened while on treatment. All fractures were considered unrelated to the study drugs by the investigators and, none resulted in discontinuation of study drugs.

Summary of Bone Mineral Density

Percentage change from baseline in hip BMD and spine BMD were the first and second key alpha-controlled safety endpoints, respectively, for both studies. Subjects receiving TAF experienced significantly less BMD reduction than those receiving TDF.

At Week 48, the mean (SD) percentage decreases from baseline were as follows:

- **Hip:** TAF −0.163% (2.2437 %); TDF −1.860 % (2.4525 %)
- **Spine:** TAF −0.570 % (2.9147 %); TDF −2.366 % (3.2051 %)

Table 1-9 presents measure of BMD at Week 48. Percentage changes from baseline in hip and spine BMD were the first and second key alpha-controlled safety endpoints in Studies GS-US-320-0108 and GS-US-320-0110. Mean percentage decreases from baseline in BMD at the hip or spine were smaller in the TAF group compared with the TDF group ($p < 0.001$). A lower percentage of subjects in the TAF group had a > 3% decrease in hip BMD compared with subjects in the TDF group (8.4% TAF; 26.7% TDF). Similarly, a lower percentage of subjects in the TAF group had a > 3% decrease in spine BMD compared with subjects in the TDF group (TAF 19.5%; TDF 38.1%). At Week 48, fewer subjects had ≥ 7% decrease in hip BMD (TAF 0.4%; TDF 2.0%) and ≥ 5% decrease in spine BMD (TAF 6.3%; TDF 20.4%) in the TAF group compared with the TDF group.

Table 1-9. GS-US-320-0108 and GS-US-320-0110: Measures of Bone Mineral Density at Week 48 (Hip DXA Analysis Set and Spine DXA Analysis Set)

	N	TAF 25 mg	N	TDF 300 mg
Hip DXA Analysis Set				
Mean (SD) Percent Change in Hip BMD	807	−0.163 (2.2437)	404	−1.860 (2.4525)
P-Value[a]	< 0.001			
Difference in LSM	1.697 (1.420, 1.974)			
Subjects with > 3% Decrease in Hip BMD, n (%)	807	68 (8.4%)	404	108 (26.7%)
P-Value[b]	< 0.001			
Subjects with > 3% Increase in Hip BMD, n (%)	807	55 (6.8%)	404	8 (2.0%)
P-Value[b]	< 0.001			
Subjects with no Decrease (≥ Zero %Change) in Hip BMD, n (%)	807	383 (47.5%)	404	83 (20.5%)
Spine DXA Analysis Set				
Mean (SD) Percent Change in Spine BMD	814	−0.570 (2.9147)	407	−2.366 (3.2051)
P-Value[a]	< 0.001			
Difference in LSM	1.796 (1.437, 2.155)			
Subjects with > 3% Decrease in Spine BMD, n (%)	814	159 (19.5%)	407	155 (38.1%)
P-Value[b]	< 0.001			
Subjects with > 3% Increase in Spine BMD, n (%)	814	89 (10.9%)	407	11 (2.7%)
P-Value[b]	< 0.001			
Subjects with no Decrease (≥ Zero %Change) in Spine BMD, n (%)	814	331 (40.7%)	407	89 (21.9%)

DXA = dual-energy x-ray absorptiometry; LSM = least-squares mean

a P-values, difference in least squares means, and its 95% CI were from the ANOVA model including treatment as a fixed effect.

b P-values were calculated from the Cochran-Mantel-Haenszel test for ordinal data (row mean scores differ statistic was used).

Source: TAF Week 48 ISS, Tables 23.1.2, 23.2.2, 25.1, and 25.2 and Request 7633 Tables 2.1 and 2.2

Renal Safety

In the TAF Phase 3 Safety Population in Studies GS-US-320-0108 and GS-US-320-0110 (TAF 25 mg N = 866, TDF 300 mg N = 432; Total N = 1301), no cases of proximal renal tubulopathy (including Fanconi syndrome) or renal failure were reported in either treatment group. No subject in the TAF Phase 3 Safety population experienced a renal SAE or AE resulting in discontinuation of study drugs while on study.

Summary of Renal Laboratory Parameters

Change from baseline in serum creatinine was the third key alpha-controlled safety endpoint. Overall, increases from baseline in mean values for serum creatinine were smaller in the TAF group compared with the TDF group. Mean (SD) changes from baseline at Week 48 were 0.010 (0.1140) mg/dL for the TAF group and 0.024 (0.0974) mg/dL for the TDF group (p = 0.012). Graded serum creatinine abnormalities were reported for 6 subjects (0.7%) in the TAF group; all of which were Grade 1 or 2. Of the 6 subjects, 5 subjects had isolated serum

creatinine elevations that were not associated with decreased eGFR. One subject, who had a relevant medical history of hypertension and diabetes, had multiple instances of graded creatinine elevations and eGFR ≤ 50 mL/min. No subjects in the TDF group had graded serum creatinine elevations.

In the TAF group, decreases from baseline in median $eGFR_{CG}$ values were significantly smaller compared with the TDF group. Median (Q1, Q3) changes from baseline at Week 48 were −1.2 (−8.4, 7.5) mL/min in the TAF group and −5.4 (−12.0, 3.0) mL/min in the TDF group ($p < 0.001$).

The overall number of subjects who had any confirmed renal laboratory abnormality (ie, confirmed increases from baseline in creatinine of at least 0.5 mg/dL, or $eGFR_{CG}$ below 50 mL/min, or confirmed phosphorus < 2 mg/dL, was small (TAF 0.6%, 5 subjects; TDF 1.6%, 7 subjects). Most instances were isolated, transient, and resolved without treatment.

Summary of Proteinuria by Urinalysis (Dipstick) and by Quantitative Assessment

A similar percentage of subjects in each treatment group had at least 1 recorded, graded proteinuria by dipstick while on study; most of which were Grade 1. Table 1-10 presents a summary of the quantitative markers of proteinuria, urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR). There was a significant difference between the 2 treatment groups in median percentage changes from baseline in 1 of the quantitative markers of proteinuria UPCR at Week 48. The median (Q1, Q3) percentage change in UPCR was 6.0 (−31.0, 57.6) mg/g in the TAF group and 16.5 (−21.6, 72.4) mg/g in the TDF group ($p = 0.010$). Although not statistically significant, the median percentage change from baseline in UACR was lower in the TAF group compared with the TDF group. Median percentage changes from baseline in the markers of proximal tubular dysfunction, urine retinol binding protein (RBP) to creatinine ratio and urine beta-2-microglobulin to creatinine ratio was smaller in the TAF group compared with the TDF group ($p < 0.001$ for the differences between the 2 groups at Weeks 24 and 48).

Table 1-10. GS-US-320-0108 and GS-US-320-0110: Renal Biomarkers to Urine Creatinine Ratios at Week 48 in the TAF Phase 3 Safety Population (Safety Analysis Set)

Parameter	Median Percentage Change (%) (Q1, Q3)		P-Value[a]
	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)	
UPCR (mg/g)	6.0 (−31.0, 57.6)	16.5 (−21.6, 72.4)	0.010
UACR (mg/g)	6.9 (−25.8, 46.7)	12.2 (−21.0, 63.5)	0.073
Urine RBP to Urine Creatinine Ratio (µg/g)	−0.3 (−23.2, 33.3)	25.1 (−7.9, 73.2)	< 0.001
Urine Beta-2-Microglobulin to Creatinine Ratio (µg/g)	−3.5 (−34.3, 32.0)	37.9 (−4.6, 152.4)	< 0.001

UACR = urine albumin to creatinine ratio; UPCR = urine protein to creatinine ratio
% Change = Change from baseline at a postbaseline visit/baseline × 100%.
a P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: TAF Week 48 ISS, Tables 34.1, 34.2, 34.3, and 34.4

Graded Laboratory Abnormalities

Most subjects participating in Studies GS-US-320-0108 and GS-US-320-0110 experienced at least 1 laboratory abnormality of Grade 1 or higher (TAF 94.8%, 814 of 859 subjects; TDF 91.1%, 390 of 428 subjects). The majority of subjects had abnormalities that were Grade 1 or 2 at worst severity (TAF 63.4%, 545 subjects; TDF 61.7%, 264 subjects). Grade 3 laboratory abnormalities occurred in 26.2% (225 subjects) in the TAF group and 22.4% (96 subjects) in the TDF group; Grade 4 laboratory abnormalities were less common, occurring in 5.1% (44 subjects) in the TAF group and 7.0% (30 subjects) in the TDF group. In total, a similar percentage of subjects in each group had at least 1 Grade 3 or 4 laboratory abnormality (TAF 31.3%, 269 subjects; TDF 29.4%, 126 subjects).

Table 1-11 presents a summary of the subject incidence of Grade 3 or 4 serum chemistry or urinalysis abnormalities reported for ≥ 1% in either treatment group for the overall TAF Phase 3 Safety Population. The only Grade 3 or 4 serum chemistry laboratory abnormality that occurred in > 5% of subjects overall in each of the treatment groups individually was ALT elevation (TAF 8.1%, 70 subjects; TDF 9.3%, 40 subjects). In the TDF group, Grade 3 or 4 elevations of AST also occurred in > 5% of subjects overall (TAF 3.3%, 28 subjects; TDF 5.4%, 23 subjects). Grade 3 urinalysis abnormalities included occult blood (TAF 7.7%, 66 subjects; TDF 7.0%, 30 subjects), urine erythrocytes (TAF 7.7%, 59 subjects; TDF 9.1%, 35 subjects), and urine glucose (TAF 4.8%, 41 subjects; TDF 1.2%, 5 subjects). The majority of subjects (88.6%; 124 of 140 subjects) who had Grade 3 urine occult blood or urine erythrocytes were women of child bearing potential (defined as age ≤ 54 years). The abnormalities were generally asymptomatic and not associated with AEs; none of the events were considered related to study drugs. Among the 41 subjects in the TAF group with Grade 3 urine glucose on treatment, 18 subjects (43.9%) had Grade 3 urine glucose at either screening or baseline, while the majority of the remaining 23 subjects 23 subjects had a medical history relevant for diabetes mellitus and/or had a graded elevation in blood glucose, or experienced an isolated and transient occurrence of Grade 3 urine glucose.

Table 1-11. GS-US-320-0108 and GS-US-320-0110: Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities Reported for at Least 1% of Subjects in Either Treatment Group in the Overall TAF Phase 3 Safety Population (Safety Analysis Set)

	TAF 25 mg (N = 866)	TDF 300 mg (N = 432)
Maximum Postbaseline Toxicity Grade (N)	859	428
Grade 3	225 (26.2%)	96 (22.4%)
Grade 4	44 (5.1%)	30 (7.0%)
Chemistry		
Alanine Aminotransferase (N)	859	428
Grade 3	52 (6.1%)	27 (6.3%)
Grade 4	18 (2.1%)	13 (3.0%)
Amylase (N)	859	427
Grade 3	22 (2.6%)	9 (2.1%)
Aspartate Aminotransferase (N)	859	428
Grade 3	25 (2.9%)	18 (4.2%)
Grade 4	3 (0.3%)	5 (1.2%)
Creatine Kinase (N)	859	428
Grade 3	16 (1.9%)	7 (1.6%)
Grade 4	9 (1.0%)	6 (1.4%)
Fasting Glucose (Hyperglycemia) (N)	857	425
Grade 3	9 (1.1%)	0
Fasting LDL Cholesterol (N)	837	417
Grade 3	37 (4.4%)	1 (0.2%)
Nonfasting Glucose (Hyperglycemia) (N)	856	426
Grade 3	25 (2.9%)	7 (1.6%)
Urinalysis		
Occult Blood (N)	859	426
Grade 3	66 (7.7%)	30 (7.0%)
Urine Erythrocytes (N)	768	386
Grade 3	59 (7.7%)	35 (9.1%)
Urine Glucose (N)	859	426
Grade 3	41 (4.8%)	5 (1.2%)

Denominator for percentage (N) is the number of subjects in the safety analysis set with at least 1 postbaseline laboratory value for the test.
Subjects were counted once for the maximum postbaseline severity for each laboratory test. For urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade is Grade 3.
For nonfasting glucose, the maximum postbaseline toxicity grades, instead of treatment-emergent abnormalities, were summarized, because nonfasting glucose test was not done at baseline.
'Hyper' means high and 'Hypo' means low.
Source: TAF Week 48 ISS, Table 20

Hepatic Laboratory Abnormalities

In Studies GS-US-320-0108 and GS-US-320-0110 the incidence of graded hepatic laboratory abnormalities through the Week 48 data cutoff date was generally lower for subjects in the TAF group compared with subjects in the TDF group, and included ALT increased (TAF 22.8%, 196 subjects; TDF 30.4%, 130 subjects), AST increased (TAF 22.2%, 191 subjects; TDF 25.2%, 108 subjects), total bilirubin increased (TAF 12.7%, 109 subjects; TDF 10.0%, 43 subjects), gamma-glutamyltransferase (GGT) increased (TAF 7.5%, 64 subjects; TDF 10.0%, 43 subjects), alkaline phosphatase increased (TAF 2.2%, 19 subjects; TDF 5.4%, 23 subjects), and albumin decreased (TAF 0.9%, 8 subjects; TDF 1.9%, 8 subjects).

Hepatic laboratory abnormalities in both treatment groups were generally Grade 1 or 2 at maximum severity; Grade 3 or 4 ALT abnormalities and Grade 3 or 4 AST abnormalities were observed in lower percentages of subjects in the TAF group compared with the TDF group (ALT: TAF 8.1%, 70 subjects; TDF 9.3%, 40 subjects; AST: TAF 3.3%, 28 subjects; TDF 5.4%, 23 subjects), while Grade 3 or 4 bilirubin elevations were observed in comparable percentages of subjects in the TAF group (0.3%, 3 subjects) compared with the TDF group (0.2%, 1 subject). Hepatic laboratory abnormalities were generally not associated with hepatic AEs.

Hepatic Flares

An ALT elevation was defined as treatment-emergent serum ALT > 2 × baseline value and > 10 × ULN, with or without associated symptoms. Through Week 48, ALT elevations were observed for 16 subjects (1.8%) in the TAF group and 9 subjects (2.1%) of subjects in the TDF group. Most of the events were at isolated time points within the first 8 weeks of dosing and resolved without recurrence while the subject remained on study drug. An ALT elevation that was confirmed at 2 consecutive postbaseline visits was considered an ALT flare. The incidence of these events was balanced between the treatment groups. Five subjects (0.6%) in the TAF group and 4 subjects (0.9%) in the TDF group had a treatment-emergent ALT flare. With the exception of 2 events, ALT flares occurred early in the dosing period; for 7 of the 9 subjects, the ALT flares resolved without recurrence while the subject remained on study drug.

Metabolic Laboratory Parameters

Administration of TDF has been associated with lower fasting low-density lipoprotein (LDL) and high-density lipoprotein (HDL) as compared with other antiviral agents. As plasma TFV exposures are approximately 90% lower with TAF administration than with TDF, fasting lipid concentrations remained relatively stable through Week 48 in the TAF treatment group, while TDF administration resulted in the expected lipid-lowering TFV effect, with decreases from baseline in fasting lipid parameters observed in the TDF group. Median decreases from baseline in total cholesterol, LDL, HDL, and triglycerides were greater in the TDF group than the TAF group, with TDF subjects demonstrating reductions in all parameters at Week 48. The difference between groups in median change from baseline was statistically significant a Week 48 for total cholesterol, direct LDL, HDL, and triglycerides ($p < 0.001$). Median (Q1, Q3) changes from baseline at Week 48 for fasting lipid parameters were as follows:

- **Total cholesterol:** TAF −2 (−17, 17) mg/dL; TDF −24 (−42, −6) mg/dL
- **LDL:** TAF 4 (−9, 20) mg/dL; TDF −9 (−25, 5) mg/dL
- **HDL:** TAF −3 (−10, 2) mg/dL; TDF −9 (−17, −3) mg/dL
- **Triglycerides:** TAF 6 (−13, 26) mg/dL; TDF −7 (−27, 10) mg/dL

The median (Q1, Q3) change from baseline at Week 48 in total cholesterol to HDL ratio was 0.2 (−0.1, 0.5) in the TAF group and 0.2 (−0.2, 0.5) in the TDF group (p = 0.16 for the difference between treatment groups).

Eight subjects (0.9%) in the TAF group had Grade 3 elevated fasting cholesterol; 7 of the 8 subjects had a history of hyperlipidemia and/or elevated fasting cholesterol at baseline. There were no subjects with Grade 4 elevated fasting cholesterol in the TAF group, and none with Grade 3 or 4 elevated fasting cholesterol in the TDF group. Thirty-seven subjects (4.4%) in the TAF group and 1 subject (0.2%) in the TDF group had Grade 3 elevated fasting LDL. Overall, changes in median values of total cholesterol, LDL, HDL, and triglycerides in the TAF group were not clinically relevant, and none of the subjects with Grade 3 elevations in fasting lipids had clinical AEs associated with lipid abnormalities.

1.3. Rationale and Risk/Benefit Assessment for this Study

While the number of liver transplants for CHB consequences is low in the United States (~350/year), in countries with high prevalence of CHB, HBV remains the most important cause of liver transplantation {Lee 2015}. Without prophylaxis, patients with CHB receiving a liver transplant have near universal re-infection of the graft {Samuel 1993}. Current practice is to treat prior and post-transplant patients with oral nucleos(t)ide polymerase inhibitors and Hepatitis B Immunoglobulin (HBIG) to prevent infection of the new liver. Study 203-0107 demonstrated in a small group of post-liver transplant patients that treatment with TDF/FTC alone was equivalent to TDF/FTC + HBIG after 72 weeks of follow-up {Teperman 2013}.With these interventions, infection of the graft has been reduced to < 10% {Katz 2010}. While practice patterns for continuation of HBIG can vary by center, all patients must remain on lifelong nucleos(t)ide analog treatment.

After receiving a liver transplant, the majority of patients develop some degree of chronic kidney disease, with over 18% having a GFR< 30 ml/min within 5 years of transplant mainly as a result of the use of calcineurin inhibitors (CNI) {Lucey 2013, Ojo 2003}. CNIs are a mainstay of immunosuppression immediately after transplantation and can lead to acute or chronic kidney injury through hemodynamic changes or direct nephrotoxic effects. While some centers reduce or eliminate CNIs from immunosuppressive regimens over time, many continue patients lifelong on CNIs. Even in those patients who stop CNIs, the renal effects are often not reversible. This persistent renal dysfunction, therefore, can complicate antiviral treatment with medications such as TDF.

For these patients who have received a liver transplant and have renal insufficiency, TAF may provide an alternative to currently used treatments by achieving viral suppression while resulting in improved safety of bone and renal parameters compared to TDF-based regimens.

1.4. Rationale for Dose Selection

A 25-mg dose of TAF was selected for use in the Phase 3 non-inferiority studies based upon the magnitude of HBV DNA decline, systemic TFV exposure, and the safety profile. In Study GS-US-320-0101, the magnitude of HBV DNA decreases observed over 28 days in subjects with CHB given TAF at doses of 8, 25, 40, and 120 mg were similar indicating a lack of dose effect; these decreases were also comparable with the TDF 300-mg dose, which is the dose of TDF approved for treatment of CHB. In subjects who received TAF 25 mg, reduced systemic TFV exposures (approximately 92%) were observed relative to those who received the TDF 300-mg dose, which is consistent with data in HIV-infected subjects who received TAF 25 mg as a single agent in Study GS-US-120-0104.

The selection of 25 mg TAF dose in this study is further supported by the results from the dedicated severe renal impairment study (GS-US-120-0108). In that study, plasma TAF exposure in subjects with severe renal impairment was less than 2-fold higher than TAF exposure in matched controls with normal renal function. For TFV, mean AUC was ~6-fold higher in renally impaired subjects as compared to matched controls. Importantly, TFV exposure was within the range of TFV exposures achieved following administration of a TDF-containing regimen in subjects with normal renal function. As such, dose adjustment of TAF in severe renal impairment was not warranted.

The PK/PD relationship between TAF plasma exposure and efficacy was also explored using data from the Phase 3 Studies GS-US-320-0108 and GS-US-320-0110. Importantly, in both studies virologic suppression (HBV DNA < 29 IU/mL) was uniform across the categories of TAF exposures, with no trends in exposure-response relationship observed.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the safety and tolerability of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in $eGFR_{CKD-EPI}$ at Week 24
- To evaluate the efficacy of TAF 25 mg QD versus TDF-containing regimens in maintaining viral suppression at Week 24

The secondary objectives of this study are:

- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the percent change from baseline in hip and spine bone mineral density (BMD) at Weeks 24 and 48
- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in serum creatinine at Weeks 24 and 48
- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in $eGFR_{CKD-EPI}$ at Week 48
- To evaluate the efficacy of TAF 25 mg QD versus TDF-containing regimens in maintaining viral suppression at Week 48

The exploratory objectives of this study are:

3. STUDY DESIGN

3.1. Endpoints

3.1.1. Primary Endpoints

The **primary safety endpoint** is:

- Change from baseline in $eGFR_{CKD-EPI}$ of TAF 25 mg QD versus TDF-containing regimens at Week 24

The **primary efficacy endpoint** is:

- Proportion of subjects with HBV DNA < 20 IU/mL at Week 24

3.1.2. Secondary Endpoints

The **secondary safety endpoints** are:

- Percent change from baseline in hip and spine bone mineral density (BMD) of TAF 25 mg QD versus TDF-containing regimens at Weeks 24 and 48
- Change from baseline in serum creatinine of TAF 25 mg QD versus TDF-containing regimens at Weeks 24 and 48
- Change from baseline in $eGFR_{CKD-EPI}$ of TAF 25 mg QD versus TDF-containing regimens at Week 48

The **secondary efficacy endpoint** is:

- Proportion of subjects with HBV DNA < 20 IU/mL at Week 48

3.1.3. Other Endpoints of Interest

The **exploratory endpoints** of this study are:

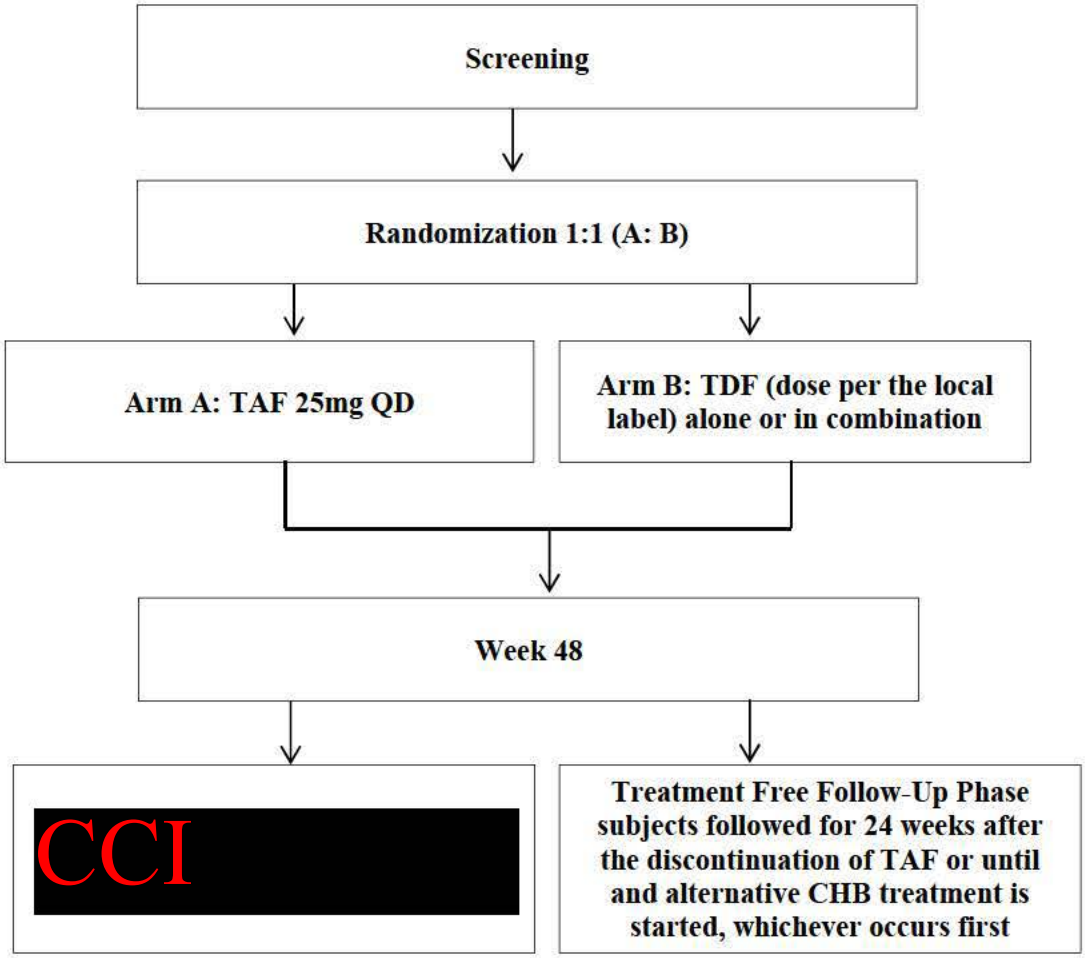
[redacted]

[redacted]

3.2. Study Design

This is a randomized, open label study to evaluate the antiviral activity of TAF 25 mg QD versus TDF (dose per the local label) containing regimens. Approximately fifty (50) adult CHB subjects with Stage 2 or greater chronic kidney disease and have received a liver transplant will be eligible for enrollment. They will be randomized in a 1:1 ratio (A: B) to the treatment arms for 48 weeks. Approximately 40 of 50 subjects will be enrolled with $eGFR_{CKD\text{-}EPI} < 60$ ml/min/1.73m^2.

Figure 3-1. Study Schema



3.3. Study Treatments

Approximately 50 subjects with CHB and Stage 2 or greater chronic kidney disease and have received a liver transplant will be assigned to one of the two treatment arms (A: B) for 48 weeks. Randomization will be stratified by baseline renal function ($eGFR_{CKD-EPI}$ < 50 ml/ min/1.73m^2 and ≥ 50 ml/ min/1.73m^2).

- **Treatment Arm A:** approximately 25 subjects administered TAF 25 mg oral daily
- **Treatment Arm B:** approximately 25 subjects to continue administration of TDF alone or in combination with other approved antivirals per local practice

3.4. Duration of Treatment

The duration of the study treatment is 48 weeks with an initial screening period of 45 days. Subsequent to Screening, subjects will be randomized to receive TAF or TDF alone or in combination with approved antivirals per local practice.

At Week 48, per Principal Investigator (PI) discretion, subjects will be eligible to receive TAF 25 mg daily and CCI [redacted] they will be followed for 24 weeks after the discontinuation of TAF (i.e., Treatment Free Follow-Up, TFFU) or until an alternative CHB treatment is started, whichever occurs first.

3.5. End of Study

The end of the study will be the last subjects' last observation or visit.

3.6. Biomarker Testing

3.6.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or adverse events and to increase knowledge and understanding of the biology of chronic hepatitis B. The specific analyses will include, but will not be limited to, the bone and renal biomarkers –such as, C-type collagen sequence (CTX) and procollagen type 1 N-terminal propeptide (P1NP), retinol binding protein and beta-2-microglobulin.

Because biomarker science is a rapidly evolving area of investigation, and adverse events in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge. Samples may be stored by Gilead Sciences for a period of 15 years.

CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 50 subjects, who are 18 years or older, with chronic hepatitis B, currently virally suppressed with Stage 2 or greater chronic kidney disease and have received a liver transplant. They will be randomized 1:1 to receive TAF 25 mg or continue with TDF alone or in combination with other approved antivirals for 48 weeks.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Must have the ability to understand and sign a written informed consent form; consent must be obtained prior to initiation of study procedures

2) Adult male or non-pregnant female subjects, over 18 years of age based on the date of the screening visit

3) Documented evidence of chronic HBV infection prior to transplantation

4) Primary or secondary (re-transplant), liver alone or liver and kidney transplant recipient from deceased or living donor

5) Liver Transplant ≥ 12 weeks prior to screening

6) Maintained on TDF alone or in combination with other approved antivirals for HBV prophylaxis or treatment

7) Have been on approved HBV OAV treatment for at least 12 weeks post-transplant prior to screening, with HBV DNA < LLOQ at screening

8) Screening $eGFR_{CKD\text{-}EPI} < 90$ ml/min/1.73m^2

9) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 6

10) Women considered of child bearing potential (see Appendix 6) must have a negative serum pregnancy test at Screening and a negative urine test at Baseline before dosing

11) Must be willing and able to comply with all study requirements

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Multi-organ transplant that includes heart or lung recipient (subjects who have their liver transplant as part of a liver-kidney dual transplant are eligible to enroll)

2) Subjects with history of de novo or recurrent hepatocellular carcinoma (HCC) post-transplant and at screening

3) Histological evidence of unresolved transplant rejection

4) Current, uncontrolled ascites, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, or other signs of decompensated cirrhosis

5) Subjects meeting any of the following laboratory parameters at screening:

   a) ALT > 10× the upper limit of normal (ULN)

   b) INR > 1.5 × ULN unless the subject is stable on anticoagulant regimen affecting INR

   c) Albumin < 3.0 g/dL

   d) Direct bilirubin ≥ 4 × ULN

   e) Platelet count < 50,000/mL

   f) $eGFR_{CKD\text{-}EPI}$ < 15 ml/min/1.73m^2

6) Subjects on hemodialysis

7) Co-infection with HIV or HCV

8) Recent (within 4 weeks of Screening) episode or infection requiring systemic antibiotics

9) Use of any prohibited medications listed in Section 5.4 within 28 days of the Baseline/Day 1 visit

10) Malignancy within 5 years prior to screening, with the exception of specific cancers that are cured by surgical resection (e.g., basal cell skin cancer, etc) or hepatocellular carcinoma. Subjects under evaluation for possible malignancy are not eligible

11) Significant cardiovascular, pulmonary, or neurological disease

12) Use of investigational agents within 3 months of screening, unless allowed by the Sponsor

13) Use of any prohibited concomitant medications as described in Table 5-1

14) Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance

15) Known hypersensitivity to study drugs, metabolites or formulation excipients

16) Lactating females or those who may wish to become pregnant during the course of the study

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, and Treatment Codes

The randomization will be performed via an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS), whereby study treatment will be assigned to subjects according to the randomization schedule. A unique subject number will be provided during randomization. Eligible subjects (n = 50) will be randomized in a 1:1 ratio to receive either TAF or continue on TDF alone or in combination with other approved antivirals for 48 weeks. Randomization will be stratified by baseline renal function ($eGFR_{CKD-EPI}$ < 50 ml/min/1.73m^2 and ≥ 50 ml/min/1.73m^2).

5.2. Description and Handling of Tenofovir Alafenamide (TAF)

5.2.1. Formulation

5.2.1.1. Tenofovir Alafenamide (TAF) Tablets

TAF 25 mg tablets contain 28 mg of tenofovir alafenamide fumarate, which is equivalent to 25 mg of tenofovir alafenamide (TAF). The tablets are yellow, round-shaped, and film-coated. The tablets are debossed with “GSI” on one side and “25” on the other side. In addition to the active ingredient, each film-coated tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

5.2.2. Packaging and Labeling

TAF tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and a silica gel desiccant and polyester material. Each bottle is enclosed with a white, continuous-thread, child-resistant polypropylene screw cap fitted with an induction-sealed, and aluminum-faced liner.

Study drug(s) to be distributed to centers in NZ and other participating countries shall be labeled to meet applicable requirements of local regulations.

5.2.3. Storage and Handling

Study drug TAF should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration of TAF

Subjects will be randomly assigned (1:1) to receive one of the following treatments:

- **Treatment Arm A:** approximately 25 subjects administered TAF 25 mg QD
- **Treatment Arm B:** approximately 25 subjects to continue administration of TDF alone or in combination with other approved antivirals alone or in combination with other approved antivirals per local practice

After 48 weeks, subjects in treatment arms A and B will be eligible to receive TAF 25 mg daily CCI [redacted]

It is preferred that subjects take their study drug according to a morning dosing schedule; however, evening dosing is allowable.

TAF tablets are to be administered orally with food, taken at approximately the same time each day.

5.4. Prior and Concomitant Medications

Concomitant/previous medications **taken within 30 days of screening**, up to and including the date of the visit 4 weeks after discontinuation of study treatment, need to be recorded in the source documents and eCRFs.

The following medications are **prohibited during the screening period and for a minimum of 28 days prior to the Day 1** visit through the end of treatment:

- Investigational agents or devices for any indication
- Nephrotoxic agents (e.g., aminoglycosides, amphoterecin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine)
- Probenecid
- Agents that reduce renal function or compete for active tubular secretion with tenofovir (e.g., cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir)
- Systemic chemotherapeutic agents

Treatment-experienced subjects (defined as subjects meeting all entry criteria [including HBV DNA and serum ALT criteria] and with ≥ 12 weeks of previous treatment with any nucleoside or nucleotide analogue) receiving oral antiviral treatment at Screening must continue their treatment regimen until the time of randomization/Baseline/Day 1, when it will be discontinued.

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e., P-gp) with study drug(s) may result in PK interactions resulting in increases or decreases in exposure of TAF.

Examples of representative medications which are prohibited or to be used with caution from 21 days prior to Day 1 through the end of treatment are listed below:

Table 5-1. Disallowed and Concomitant Medications to Be Used with Caution

Medication Class	Prohibited Medications	Medications to Be Used with Caution
Anticonvulsants[a]		Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin
Antifungals[b]		Itraconazole, Ketoconazole
Antimycobacterials[a]	Rifapentine, Rifabutin, Rifampin	
Herbal/Natural Supplements[a]	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	

a May result in a decrease in the concentration of TAF
b May result in an increase in the concentrations of TAF

Should subjects have a need to initiate treatment with any excluded concomitant medication, including herbal/natural products/therapies, and over the counter medications, the Gilead Sciences Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the investigator must notify Gilead Sciences as soon as he/she is aware of the use of the excluded medication.

5.5. Accountability for Tenofovir Alafenamide (TAF)

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused IMP. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP dispensed to subjects must be returned to the site.

Investigational product accountability records will be provided to the study site to:

- Record the date received and quantity of IMP kits and/or bottles
- Record the date, subject number, subject initials, the IMP kit and/or bottles number dispensed
- Record the date, quantity of used and unused IMP kit and/or bottles returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

At the start of the study, the study monitor will evaluate the study center's study drug disposal procedures and provide appropriate instruction for return or destruction of unused study drug supplies. If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used and unused study drug supplies performed in accordance with the site's (hospital/pharmacy) SOP. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies. A copy of the site's SOP will be obtained for central files. Where possible, study drug will be destroyed at the site. Upon study completion, a copy of the Investigational Drug Accountability records must be filed at the site. Another copy will be returned to Gilead Sciences. If drug is destroyed on site, the investigator must maintain accurate records for all study drug kits and/or bottles destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug. All study drug records must be maintained at the site and copies must be submitted to Gilead Sciences at the end of the study.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the sponsor.

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to enrollment. Once consent has been obtained, all screening tests and procedures have been completed, and study eligibility has been confirmed, subjects will be randomized within 45 days using an IVRS/IWRS. Subjects will receive study drugs within their assigned treatment group as described in Section 3.2. Candidates who fail to meet eligibility criteria by screening evaluations may be re-screened once after the initial screen if there is a reasonable expectation that the candidate will be eligible after repeat screening.

Retesting of an exclusionary laboratory value during the Screening period is permitted only if in the Principal Investigator's opinion, the retest value will be within accepted parameters; if the initial value was deemed to be inaccurate, inconsistent with the subject's previous result(s); in error (e.g. mishandled sample); or due to an extenuating circumstance.

6.2. Pretreatment Assessments

Prior to the conduct of any screening procedures, each candidate must sign an Informed Consent Form. Consent is to be obtained in accordance with regulatory and local Ethics Committee requirements.

6.2.1. Screening Visit (Day −45 to Day 1 of Treatment)

Subjects will be screened within 45 days before randomization to determine eligibility for participation in the study. The following will be performed and documented at screening:

[redacted]

- Obtain medical history, including Hepatitis B history and treatment history
- Review of inclusion/exclusion criteria

- Review of AEs and concomitant medications
- Perform complete physical examination including, vital signs (blood pressure, pulse, respiration rate and temperature), body weight, and height
- Perform DXA scan of spine and hip. DXA scan will be performed at any time during the Screening period and should be completed at least 14 days prior to the first dose of the study drug, in order to ensure an acceptable pre-dose DXA scan
- Obtain blood samples for laboratory assessments as follows:
  - Safety laboratory tests (serum chemistry, hematology, and coagulation)
  - Quantification of plasma HBV DNA levels
  - Qualitative HBsAg and HBeAg (HBsAb and HBeAb reflex testing will be performed as needed)
  - Other viral serology (HCV, HIV and HDV)
  - $eGFR_{CKD\text{-}EPI}$
  - Serum β-hCG pregnancy test (for all female subjects of child-bearing potential)
  - Alpha-fetoprotein (AFP). Subjects with an AFP >50 ng/mL or other findings concerning HCC must have an appropriate evaluation (e.g., CT scan) to rule out HCC prior to being able to enter into the study
- Obtain urine sample for urinalysis, and urine drug screen
- Record any serious adverse events (SAE) and all adverse events (AE) related to protocol mandated procedures occurring after signing of the consent form.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 45 days after screening for randomization into the study.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Baseline Assessments (Day 1)

All baseline tests and procedures must be completed prior to the receipt of the first dose of study drug. Subjects screened within 45 days before Baseline will be eligible to participate in the study. Initiation of treatment with study drug should take place on the day of the Baseline visit. The following will be performed at the Baseline visit:

- Review of medical history, HBV history and HBV treatment history on any changes since screening visit
- Provide Health Related Quality of Life surveys (HRQoL): SF-36, CLDQ, WPAI to be completed by subjects at visit
- Perform complete physical examination including, vital signs (blood pressure, pulse, respiration rate and temperature), and body weight
- Review of inclusion/exclusion criteria
- Review of AEs and concomitant medication
- Complete the "Fracture Risk Assessment" (FRAX®) eCRF
- Cr EDTA Renal Scan
- Obtain blood samples for laboratory assessments as follows:
  - Safety laboratory tests (serum chemistry, hematology, and coagulation)
  - Quantification of plasma HBV DNA levels
  - Qualitative HBsAg and HBeAg (HBsAb and HBeAb reflex testing will be performed as needed)
  - $eGFR_{CKD\text{-}EPI}$
  - Blood sample for Vitamin D assessment
  - Blood sample for Fibrotest®
  - Blood sample for PBMC
  - Blood sample for PK
  - CCI [redacted]
  - HBV resistance surveillance

- Randomization
- Fasting blood sample for bone, renal biomarkers and metabolic assessment (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) − no food or drinks, except water, at least 8 hours prior to blood collection
- Fasting urine sample for renal biomarkers
- [redacted]
- Pregnancy test (for females of child-bearing potential; in case of a positive urine test, a serum pregnancy test will be done)
- [redacted]

6.3. Treatment Assessments

6.3.1. Study Week Assessments (Weeks 4-48)

The following evaluations will be performed at Weeks 4-48 unless specified;

- Provide Health Related Quality of Life surveys (HRQoL): SF-36, CLDQ, WPAI to be completed by subjects at visit (**Weeks 24, and 48 only**)
- Perform complete physical examination including, vital signs (blood pressure, pulse, respiration rate and temperature), and body weight (**Weeks 12, 24, and 48 only**)
- Perform symptom-driven physical examination including vital signs, and body weight (**Weeks 4, 8, 20, and 36 only**)
- Review of AEs and concomitant medications
- Cr EDTA Renal Scan (**Week 48 only**)
- Perform DXA scan of spine and hip (**Weeks 24 and 48 only**)
- Perform study drug accountability
- Dispense study drugs

- Obtain blood samples for laboratory assessments as follows:
  - Safety laboratory tests (serum chemistry, hematology, and coagulation)
  - Quantification of plasma HBV DNA levels
  - Qualitative HBsAg and HBeAg (HBsAb and HBeAb reflex testing will be performed as needed) (**Weeks 24 and 48 only**)
  - $eGFR_{CKD\text{-}EPI}$
  - Blood sample for Fibrotest® (**Weeks 24 and 48 only**)
  - Blood sample for Vitamin D assessment (**Weeks 24 and 48 only**)
  - Blood sample for AFP (**Weeks 24 and 48 only**)
  - Blood sample for PK
  - CCI [redacted]
  - Blood sample for PBMC (**Weeks 24 and 48 only**)
  - CCI [redacted]
  - HBV resistance surveillance
- Dose in clinic and collect single blood sample for plasma PK between 15 minutes to 4 hours post-dose. Subjects who elect to dose in the evening the previous day are not required to have in-clinic dosing, the plasma PK samples from these subjects can be collected anytime (not timed) (**Weeks 8 and 24 only**)
- Urine pregnancy test (for all female subjects of child-bearing potential)
- Urinalysis (**Weeks 4, 12, 24, and 48 only**)
- Fasting blood sample for bone and renal biomarkers − no food or drinks, except water, at least 8 hours prior to blood collection (**Weeks 4, 12, 24, and 48 only**)
- Fasting urine sample for renal biomarkers (**Weeks 4, 12, 24, and 48 only**)
- Fasting blood sample for metabolic assessment (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) − no food or drinks, except water, at least 8 hours prior to blood collection (**Weeks 24 and 48 only**)

[redacted]

CCI [redacted]

[redacted]

[redacted]

6.3.3. Early Discontinuation (ED) Visit

The ED visit should be performed within 14 days from notification of study discontinuation

- Provide Health Related Quality of Life surveys (HRQoL): SF-36, CLDQ, WPAI to be completed by subjects
- Perform complete physical examination including, vital signs (blood pressure, pulse, respiration rate and temperature), and body weight

- Review of AEs and concomitant medications
- Perform DXA scan of spine and hip
- Perform study drug accountability
- Obtain blood samples for laboratory assessments as follows:
  - Safety laboratory tests (serum chemistry, hematology, and coagulation)
  - Quantification of plasma HBV DNA levels
  - Qualitative HBsAg and HBeAg (HBsAb and HBeAb reflex testing will be performed as needed)
  - $eGFR_{CKD\text{-}EPI}$
  - Blood sample for Fibrotest®
  - Blood sample for Vitamin D assessment
  - Blood sample for AFP
  - CCI [redacted]
  - HBV resistance surveillance
- Urine pregnancy test (for all female subjects of child-bearing potential)
- Urinalysis
- Fasting blood sample for bone and renal biomarkers − no food or drinks, except water, at least 8 hours prior to blood collection
- Fasting urine sample for renal biomarkers
- Fasting blood sample for metabolic assessment (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) − no food or drinks, except water, at least 8 hours prior to blood collection

6.4. Post-Treatment Assessments

6.4.1. All Other Subjects Who Discontinue TAF

Subjects who have received at least one dose of TAF and discontinue treatment prematurely CCI [redacted] will be followed every 4 weeks for 24 weeks off treatment in accordance with TFFU schedule of assessments or until initiation of alternative CHB therapy, whichever comes first.

6.4.1.1. Treatment Free Follow-Up (TFFU) Visit Assessments (± 7 Days)

The following evaluations will be performed at follow up visits for subjects when they discontinue TAF unless otherwise specified. For more details, refer to Appendix 2.

- Review of AEs and concomitant medications
- Symptom-directed physical examination
- Collect vital signs and body weight
- Urine pregnancy test (for all female subjects of child-bearing potential)
- Urinalysis
- Obtain blood samples for laboratory assessments as follows:
  - Serum chemistry, hematology and coagulation tests
  - Quantification of plasma HBV DNA levels
  - Qualitative HBsAg and HBeAg (HBsAb and HBeAb reflex testing will be performed as needed)
  - $eGFR_{CKD\text{-}EPI}$
  - CCI [redacted]
  - HBV resistance surveillance

6.5. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.6, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.6. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subjects with confirmed $eGFR_{CKD\text{-}EPI}$ of < 15 mL/min/1.73m^2 at any time during the study will have their study drug permanently discontinued
- Lack of efficacy (virologic failure)
- HBsAg loss with seroconversion to anti-HBs. These subjects should discontinue study drug within 3-6 months following confirmation of seroconversion to anti-HBs. Subjects with HBsAg loss with confirmed seroconversion before Week 48 are not permitted to discontinue study drug prior to the Week 48 visit
- Discontinuation of study drug for subjects experiencing HBsAg-loss with confirmed seroconversion to anti-HBs, who have known bridging fibrosis or cirrhosis, should be considered on a case by case basis
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 6
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.9. Resistance Surveillance

Sequence analysis of the HBV polymerase/reverse transcriptase (pol/RT) for resistance mutations may be attempted for all viremic subjects (HBV DNA ≥ 69 IU/mL). As it may not be known at the time of the visit whether a patient is viremic or if it will be their last study visit, a separate virology sample for potential resistance surveillance will be collected at each study visit.

6.10. End of Study

The end of this study will be the last subject's last observation (or visit).

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (i.e., anemia) not the laboratory result (i.e., decreased hemoglobin).

Severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 5). For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub investigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (e.g., venipuncture)

7.2.2. Assessment of Severity

Severity of adverse events is to be determined based on GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 5). A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as Grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event: both AEs and SAEs can be assessed as Grade 4. An event is defined as "serious" when it meets one of the predefined outcomes described above in Section 7.1.2.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study IMP. AEs must be reported to the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the protocol–required post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead Pharmacovigilance and Epidemiology (PVE), previously known as Drug Safety and Public Health, as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up 30 days period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, i.e., the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead PVE:	Fax:	PPD
	Email:	PPD
Medical Monitor:	Name:	PPD
	Telephone:	PPD
	Fax:	PPD
	Email:	PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Toxicity Management

- All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 4.
- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice.
- Clinical events and clinically significant laboratory abnormalities will be graded according to the Table for GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 5)
- When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose or modified dose that is dependent upon discussion with the Gilead Sciences Medical Monitor
- Any recurrence of the investigational medicinal product-related Grade 3 or 4 clinical or clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of investigational medicinal product
- Administration of study drug may be discontinued due to a clinical or laboratory event. The Gilead Medical Monitor should be consulted prior to dose discontinuation of study drug unless the investigator believes that immediate action is warranted to ensure the continued safety of subject
- Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue investigational medicinal product at the discretion of the investigator.

7.5.2. Grade 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.

- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation.

7.5.3. Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

- Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., Grade 4 CK after strenuous exercise, or triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product.

7.5.4. Management of Bone Evaluation

As there is uncertainty surrounding the clinical significance and management of decreases in bone mineral density for chronic HBV-infected patients, Gilead recommends that any subject who has a DXA scan that demonstrates a decrease from baseline of > 5% in bone mineral density of the spine region or the hip region be followed per local medical practice at the discretion of the investigator.

7.5.5. Management of Potential Nephrotoxicity

$eGFR_{CKD-EPI}$ will be followed post-baseline during the study. All subjects on treatment with baseline $eGFR_{CKD-EPI}$ ≥50 mL/min/1.73m^2 that decline to <50 mL/min/1.73m^2 at any post-baseline visit and those with a post-baseline $eGFR_{CKD-EPI}$ < 30 mL/min/1.73m^2 regardless of baseline $eGFR_{CKD-EPI}$ should have serum creatinine measured again within 3 calendar days of receipt of results. At the time of this repeat serum creatinine assessment, Cystatin C will also be measured and the estimated glomerular filtration rate (eGFR) by CKD-EPI (cystatin C) will be calculated and compared with the baseline measurement of this parameter.

7.5.5.1. For subjects on TDF:

- For subjects with baseline $eGFR_{CKD-EPI}$ ≥ 50 mL/min/1.73m^2 that decline to < 50 mL/min/1.73m^2 at any post-baseline visit:
  - If the $eGFR_{CKD-EPI}$ is confirmed to be ≥ 30 mL/min/1.73m^2 and < 50 mL/min/1.73m^2, the subject will be required to undergo dose modification to every other day dosing of TDF
  - If the $eGFR_{CKD-EPI}$ is confirmed to be ≥ 30 mL/min/1.73m^2 and < 50 mL/min/1.73m^2, and the subject has undergone dose modification to every other day dosing of TDF and subsequently develops a confirmed $eGFR_{CKD-EPI}$ ≥ 50 mL/min/1.73m^2, the subject may revert to once daily dosing of TDF after discussion with the Gilead Medical Monitor
- For all subjects with a post-baseline $eGFR_{CKD-EPI}$ < 30 mL/min/1.73 m^2 and ≥ 15 mL/min/1.73 m^2:
  - If the $eGFR_{CKD-EPI}$ is confirmed to be < 30 mL/min/1.73m^2 and ≥ 15 mL/min/1.73 m^2, the subject will be required to undergo dose modification to every 96 hours dosing of TDF
  - If the $eGFR_{CKD-EPI}$ is confirmed to be < 30 mL/min/1.73 m^2 and ≥15 mL/min/1.73 m^2, and the subject has undergone dose modification to once every 96 hours dosing of TDF and subsequently develops a confirmed CLCr ≥ 30 mL/min/1.73 m^2, the subject may revert to every other day dosing of study drug after discussion with the Gilead Medical Monitor
- For all subjects with a post-baseline $eGFR_{CKD-EPI}$ < 15 mL/min/1.73 m^2:
  - If the $eGFR_{CKD-EPI}$ is confirmed to be <15 mL/min/1.73 m^2, the subject will be required to permanently discontinue treatment according to Section 7.5.5.3

7.5.5.2. For subjects on TAF:

- If the $eGFR_{CKD-EPI}$ is confirmed to be ≥ 15 mL/min/1.73 m^2, no dose modifications are required

7.5.5.3. For subjects on TAF or TDF:

- All subjects with a confirmed $eGFR_{CKD-EPI}$ < 15 mL/min/1.73 m^2 will be required to permanently discontinue treatment

- All subjects with a change from baseline serum creatinine of ≥ 0.4 mg/dL must have serum creatinine repeated, with a concurrent urinalysis and urine chemistry, within two weeks of receipt of results

7.5.6. On-Treatment ALT Flare and Post-Treatment Exacerbation of Hepatitis Management

On-Treatment ALT Flare is defined as:

- Confirmed (within 3 days of receipt of initial laboratory results) serum ALT > 2 × baseline value and > 10 × ULN, with or without associated symptoms

7.5.6.1. Management of ALT Flare in Subjects Receiving Study Medication

If laboratory results indicate elevation of ALT > 2 × baseline and > 10 × ULN, the following is recommended:

- Schedule the subject to return to the clinic as soon as possible (ideally within 3 days after initial laboratory results were drawn). During the visit, a clinical assessment of the subject will be performed. The assessment should include a physical examination and evaluation of the subject's mental status.

- Check the following laboratory parameters: serum ALT and AST, total bilirubin, INR, and serum albumin.

- If the ALT elevation is confirmed, the central clinical laboratory will conduct reflex testing for plasma HBV DNA, serology for HBV (HBsAg and HBsAb), HDV, HAV IgM, HCV, and HEV.

Based on the results of the confirmatory tests, the following treatment modifications are recommended:

Elevated Liver Enzymes, Normal or Stable relative to baseline Liver Function Tests

If ALT levels are elevated (i.e., > 2 × baseline and > 10 × ULN) with normal or stable total bilirubin and INR relative to baseline, the subject may remain on study medication and should be monitored weekly as long as ALT levels return to normal or baseline level.

During monitoring, if the ALT values remain persistently elevated, the investigator should discuss with the Gilead Medical Monitor whether the study drug should be discontinued.

For subjects with bridging fibrosis or cirrhosis, study drug discontinuation with treatment-free follow-up is to be avoided due to the potential risk of exacerbation of hepatitis in the setting of low hepatic reserve which could lead to decompensation. Subjects with bridging fibrosis or cirrhosis should be placed on commercially available HBV therapy following study drug discontinuation.

Elevated Liver Enzymes, Elevated Liver Function Tests

If ALT values are elevated (i.e., > 2 × baseline and > 10 × ULN), and total bilirubin is confirmed to be 2 × baseline value, and INR is 0.5 above baseline, provided both are > ULN, the investigator should consider discontinuing study medication (upon discussion with the Gilead Medical Monitor, unless the safety of the subject is of immediate concern).

The subject should be monitored weekly as long as ALT, total bilirubin, and INR values remain elevated or above baseline values.

During monitoring, if the ALT values and the liver function tests remain persistently elevated, the investigator should discuss with the Gilead Medical Monitor whether the study drug should be discontinued.

For subjects with bridging fibrosis or cirrhosis, study drug discontinuation with treatment-free follow-up is to be avoided due to the potential risk of exacerbation of hepatitis in the setting of low hepatic reserve which could lead to decompensation. Subjects with bridging fibrosis or cirrhosis should be placed on commercially available HBV therapy following study drug discontinuation.

7.5.6.2. Management of Exacerbation of Hepatitis in Subjects Who Have Discontinued Study Medication

If laboratory results indicate (1) an ALT elevation > 2 × baseline and > 10 × ULN alone OR associated with (2) abnormal laboratory parameters suggestive of worsening hepatic function (total bilirubin 2 × baseline, INR 0.5 above baseline, provided both are > ULN) and the subject is on no post-study therapy for HBV, the following is recommended:

- Schedule the subject to return to the clinic as soon as possible (ideally no later than 3 days after the initial laboratory values were drawn). During the visit, perform a clinical assessment of the subject.
- Check the following laboratory parameters: serum ALT and AST, total bilirubin, INR, and albumin.
- If the ALT elevation is confirmed, the central clinical laboratory will conduct reflex testing for plasma HBV DNA, serology for HBV (HBsAg and HBsAb), HDV, HAV IgM, HCV and HEV. If Plasma HBV DNA is increasing, the investigator should consider immediate initiation of approved therapy.
- The subject should be followed until laboratory parameters (ALT, total bilirubin, INR) return to normal or baseline up to a maximum of 6 months after the initial occurrence of the event.

7.5.7. Management of Ocular Safety

In a nine-month toxicology study conducted in dogs, some animals administered the highest dose of TAF (12-18mg/kg) had minimal mononuclear cell infiltration in the posterior uvea, considered secondary to general debilitation; this finding did not occur in animals given lower doses and it has not occurred in other animal studies. In the TAF HIV program, there is one report of SAEs of Grade 1 visual impairment and Grade 2 autoimmune uveitis in a 13 year-old female subject from Uganda in Study GS-US-292-0106. Onset of both events was Day 14 and both were considered related to study drug (E/C/F/TAF) by the investigator. The SAE of autoimmune uveitis resolved on Day 166, and the visual impairment was ongoing at Day 418 of study drug treatment.

Across the TAF HBV Phase 3 Safety Population, eye disorders were uncommon and balanced between the treatment groups. None were indicative of posterior uveitis, and none resulted in permanent discontinuation of study drug. Nonetheless, if any subject participating in this study develops signs or symptoms of posterior uveitis, investigators should contact the Gilead Medical Monitor to discuss the need for additional ophthalmologic evaluation including dilated fundoscopy and optical coherence tomography (OCT).

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE, , and AE in an infant following exposure from breastfeeding.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the duration of the study, including the protocol – required post treatment follow-up period, to the Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE. The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows: Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours throughout the duration of the study, including the protocol–required post treatment follow-up period. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD Refer to Appendix 6 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All special situations reports (SSRs) will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Special Situations Report (eSSR) Reporting Process

- Site personnel record all SSR data in the eCRF database and from there transmit the SSR information to Gilead PVE within 24 hours of the investigator's knowledge of the event throughout the duration of the study, including the protocol–required post treatment follow-up period. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SSR information electronically, i.e., the eCRF database is not functioning, record the SSR on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead PVE:	Email: Fax:	PPD PPD
Gilead Medical Monitor:	Name: Phone: Fax: Email:	PPD PPD PPD PPD

- As soon as it is possible to do so, any SSR reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

- Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

- Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are:

- To evaluate the safety and tolerability of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in $eGFR_{CKD\text{-}EPI}$ at Week 24
- To evaluate the efficacy of TAF 25 mg QD versus TDF-containing regimens in maintaining viral suppression at Week 24

The secondary objectives of this study are:

- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the percent change from baseline in hip and spine bone mineral density (BMD) at Weeks 24 and 48
- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in serum creatinine at Weeks 24 and 48
- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in $eGFR_{CKD\text{-}EPI}$ at Week 48
- To evaluate the efficacy of TAF 25 mg QD versus TDF-containing regimens in maintaining viral suppression at Week 48

The exploratory objectives of this study are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

8.1.2. Primary Endpoint

The **primary safety endpoint** is:

- Change from baseline in $eGFR_{CKD-EPI}$ of TAF 25 mg QD versus TDF-containing regimens at Week 24

The **primary efficacy endpoint** is:

- Proportion of subjects with HBV DNA < 20 IU/mL at Week 24

8.1.3. Secondary Endpoint

The **secondary safety endpoints** are:

- Percent change from baseline in hip and spine bone mineral density (BMD) of TAF 25 mg QD versus TDF-containing regimens at Weeks 24 and 48
- Change from baseline in serum creatinine of TAF 25 mg QD versus TDF-containing regimens at Weeks 24 and 48
- Change from baseline in serum $eGFR_{CKD-EPI}$ of TAF 25 mg QD versus TDF-containing regimens at Week 48

The **secondary efficacy endpoint** is:

- Proportion of subjects with HBV DNA < 20 IU/mL at Week 48

8.1.4. Other Endpoints of Interest

The **exploratory endpoints** are:

[redacted]

[redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analysis is the Full Analysis Set (FAS), defined as all randomized subjects who receive at least one dose of study drug. Subjects will be analyzed according to the randomized treatment assignment.

8.2.1.2. Safety

The primary analysis set for safety analyses is the Safety Analysis Set (SAS), defined as all randomized subjects who receive at least one dose of study drug. Subjects will be analyzed according to the treatment actually received. All data collected during treatment will be included in the safety summaries. Data collected during TFFU will be summarized or listed separately.

8.2.1.3. Pharmacokinetics

The PK analysis set will include all subjects who are randomized and have received at least one dose of study medication and for whom concentration data of any analytes of interest (eg, TAF and TFV) are available. The PK analysis set will be used for analyses of concentration data.

[redacted]

8.2.1.4. Biomarkers

The Biomarker analysis set will include all subjects who have evaluable biomarkers data.

8.3. Data Handling Conventions

For the primary endpoint missing data will be handled using a missing = failure approach, unless otherwise specified.

For key secondary safety endpoints, an analysis will be performed using the Last Observation Carried Forward (LOCF) method to impute the missing data.

For other categorical secondary efficacy endpoints, missing data will be handled using a missing = failure approach. For the drug resistant mutations endpoint, a missing = excluded approach will be employed.

Sensitivity analyses will be performed as warranted.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods by treatment group and overall.

Demographic summaries will include sex, race/ethnicity, and age.

Baseline data will include a summary of body weight, height, body mass index, $\log_{10}$ HBV DNA level, years positive for HBV, ALT level (≤ ULN, > ULN), previous oral nucleoside/nucleotide treatment experience, previous interferon experience, and genotype.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy analysis will be conducted when the study subjects complete 24 weeks of the treatment period or discontinue prematurely. The response rate of each treatment arm will be presented. A two-sided 95% confidence interval, adjusted for the randomization stratification factor (the adjusted Mantel-Haenszel proportions), for the difference (TAF – TDF) in the proportion of subjects who maintained viral suppression (HBV DNA < 20 IU/mL) at Weeks 24 and 48 will be constructed.

8.5.2. Secondary Analyses

The approach used for primary efficacy analysis will be applied for secondary efficacy endpoint as in Section 8.5.1.

8.6. Safety Analysis

All safety data collected on or after the date that IMP was first dispensed up to the date of last dose of IMP will be summarized by treatment group (according to the IMP received). Data for the pretreatment and TFFU periods will be included in data listings.

8.6.1. Primary Safety Analysis

The change from baseline in $eGFR_{CKD\text{-}EPI}$ at Week 24 will be summarized.

8.6.2. Secondary Safety Analyses

The change from baseline in $eGFR_{CKD\text{-}EPI}$ at Week 48 will be performed.

The percent change from baseline in hip and spine BMD at Weeks 24 and 48 will be summarized.

The change from baseline in serum creatinine at Weeks 24 and 48 will be summarized.

8.6.3. Extent of Exposure

A subject's extent of exposure to IMP data will be generated from the IMP administration data. Exposure data will be summarized by treatment group.

8.6.4. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event that begins on or after the date of first dose of treatment up to the date of last dose of treatment. Continuing adverse events diagnosed prior to the start of treatment and worsening in severity grade, or non-serious adverse events at baseline which become serious, or adverse events resulting in treatment discontinuation after the start of treatment will also be considered treatment-emergent.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC, and PT) will be provided by treatment group.

8.6.5. Laboratory Evaluations

Selected laboratory data (using units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 5.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to and including the date of last dose of treatment will be summarized by treatment group. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of treatment or after the subject has been discontinued from treatment will be included in a data listing.

8.7. Pharmacokinetic Analysis

Pharmacokinetic parameters will be listed and summarized for TAF and TFV using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Plasma concentrations of TAF and TFV over time will be plotted in semi logarithmic and linear formats as mean ± standard deviation.

CCI [redacted]

8.8. Biomarker Analysis

Selected bone biomarkers, including C-type collagen sequence (CTX) and procollagen type 1 N-terminal propeptide (P1NP), and selected renal biomarkers, including urine retinol binding protein, and urine beta-2-microglobulin, will be summarized by treatment group and visit using descriptive statistics.

8.9. Sample Size

This is an exploratory study. No formal sample size calculation was performed.

8.10. Data Monitoring Committee

A data monitoring committee (DMC) will review the progress of the study and perform review of safety data once after 30 subjects have completed 12 weeks of treatment, and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design. Subsequent meetings will be held on an ad hoc basis.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person

conducting the consent discussion, and also by an impartial witness if required by IEC or local requirements. CCI [redacted]

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, the IRB/IEC or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions in the lab manual. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF/eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled

- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect

the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g., data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead , the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB/IEC, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IEC in accordance with local requirements and receive documented IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g., attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the CRF/eCRF.

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2, Randomized, Open Label Study to Evaluate the Efficacy and Safety of Tenofovir Alafenamide (TAF) versus Tenofovir Disoproxil Fumarate (TDF)–containing Regimens in Subjects with Chronic HBV Infection and Stage 2 or Greater Chronic Kidney Disease Who Have Received a Liver Transplant

GS-US-320-3912, Amendment 3, 18 June 2019

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

PPD

Author

18 June 2019
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

	Screening (−45 Days)	BL	4	4 + 24 Hrs	8	8 + 24 Hrs	12	20	24	36	48	CCI	ED	TFFU[q]
	Visit Windows[a]		± 3 Days											± 7 Days
Written Informed Consent	X													
Review of Inclusion/Exclusion Criteria	X	X												
Medical History, including HBV history	X	X												
Review Concomitant Medications	X	X	X		X		X	X	X	X	X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X		X	X
Complete Physical Examination including vital signs, and weight	X	X					X		X		X		X	
Height	X													
Symptom-directed Physical Exam			X		X			X		X				X
Body weight	X	X	X		X		X	X	X	X	X		X	X
Vital Signs[b]	X	X	X		X		X	X	X	X	X		X	X
Randomization		X												
DXA[c] (spine & hip)	X								X		X		X	
FRAX® Fracture Risk Assessment Tool		X												

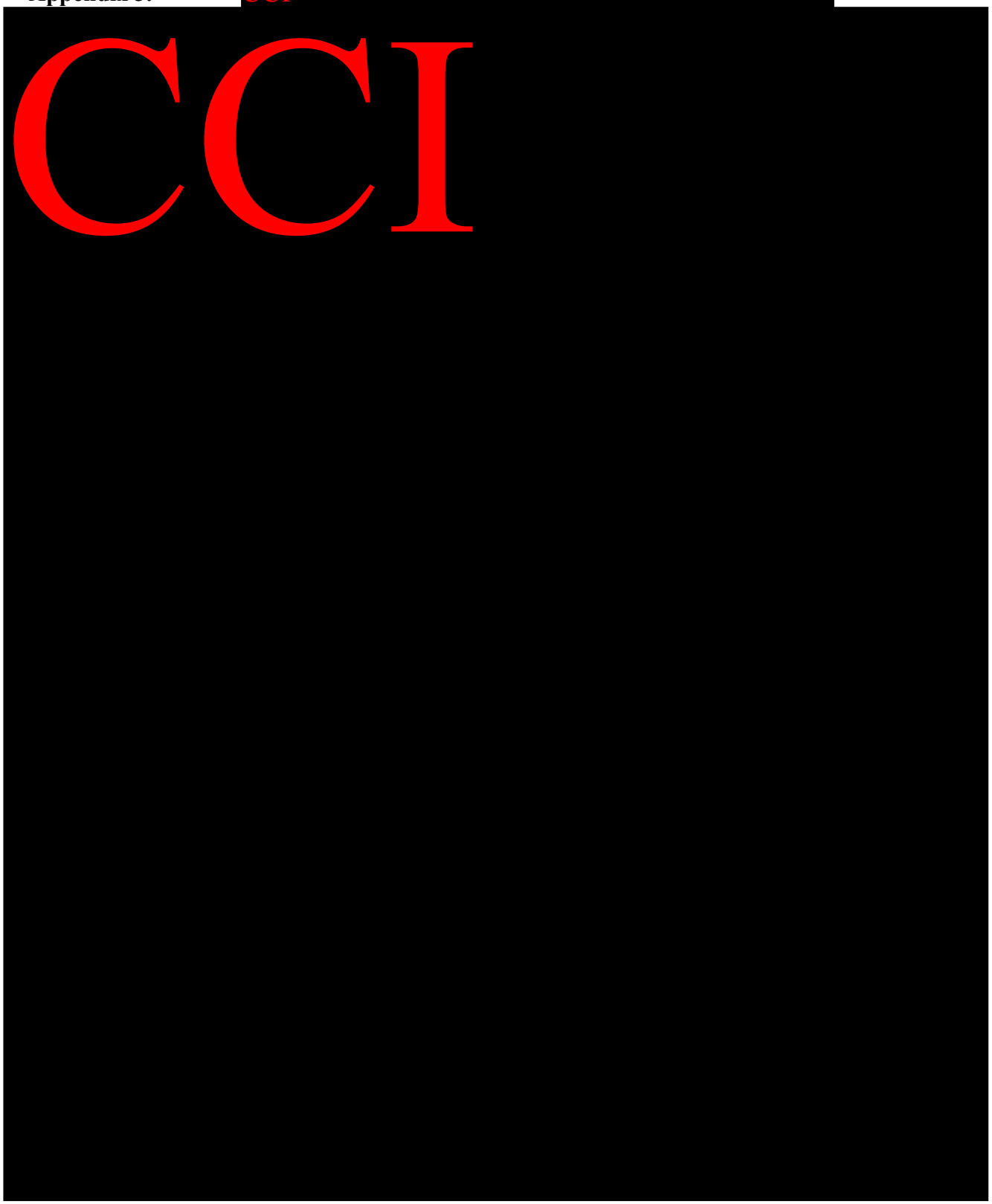
	Screening (−45 Days)	BL	4	4 + 24 Hrs	8	8 + 24 Hrs	12	20	24	36	48	CCI	ED	TFFU[q]
	Visit Windows[a]		± 3 Days											± 7 Days
Cr EDTA renal scan		X									X			
Study Drug Accountability			X		X		X	X	X	X	X		X	
Study Drug Dispensed/Retrieved		X	X		X		X	X	X	X	X		X	
Dosing in-clinic[d]			X		X									
Serum Chemistry and Liver Function Tests[e]	X	X	X		X		X	X	X	X	X		X	X
$eGFR_{CKD-EPI}$	X	X	X		X		X	X	X	X	X		X	X
Hematology	X	X	X		X		X	X	X	X	X		X	X
Cystatin C (for estimated GFR)	X	X	X				X		X		X		X	X
Plasma HBV DNA Levels	X	X	X		X		X	X	X	X	X		X	X
Serum HBsAg (qualitative)[f]	X	X							X		X		X	X
Serum HBeAg (qualitative)[f]	X	X							X		X		X	X
Sample collection for HBV Resistance Surveillance[g]		X	X		X		X	X	X	X	X		X	X
HIV-1, HDV, HCV	X													
α-fetoprotein	X								X		X		X	
Fibrotest®		X							X		X		X	
Vitamin D		X							X		X		X	

	Screening (−45 Days)	BL	4	4 + 24 Hrs	8	8 + 24 Hrs	12	20	24	36	48	CCI	ED	TFFU[q]
	Visit Windows[a]		± 3 Days											± 7 Days
Whole blood for PBMC		X							X		X			
Plasma PK[m]		X	X		X		X	X	X	X	X			
Fasting Blood for Bone Biomarkers[h]		X	X				X		X		X		X	
Fasting Blood for Renal Biomarkers[h]		X	X				X		X		X		X	
Fasting Urine for Renal Biomarkers[i]		X	X				X		X		X		X	
Fasting Metabolic Panel[o]		X							X		X		X	
Serum Pregnancy Test[j]	X													
Urine Pregnancy Test[j]		X	X		X		X	X	X	X	X		X	X
Urinalysis	X	X	X				X		X		X		X	X
Urine drug screen	X													
CCI														
Health Related Quality of Life Surveys[l]		X							X		X		X	

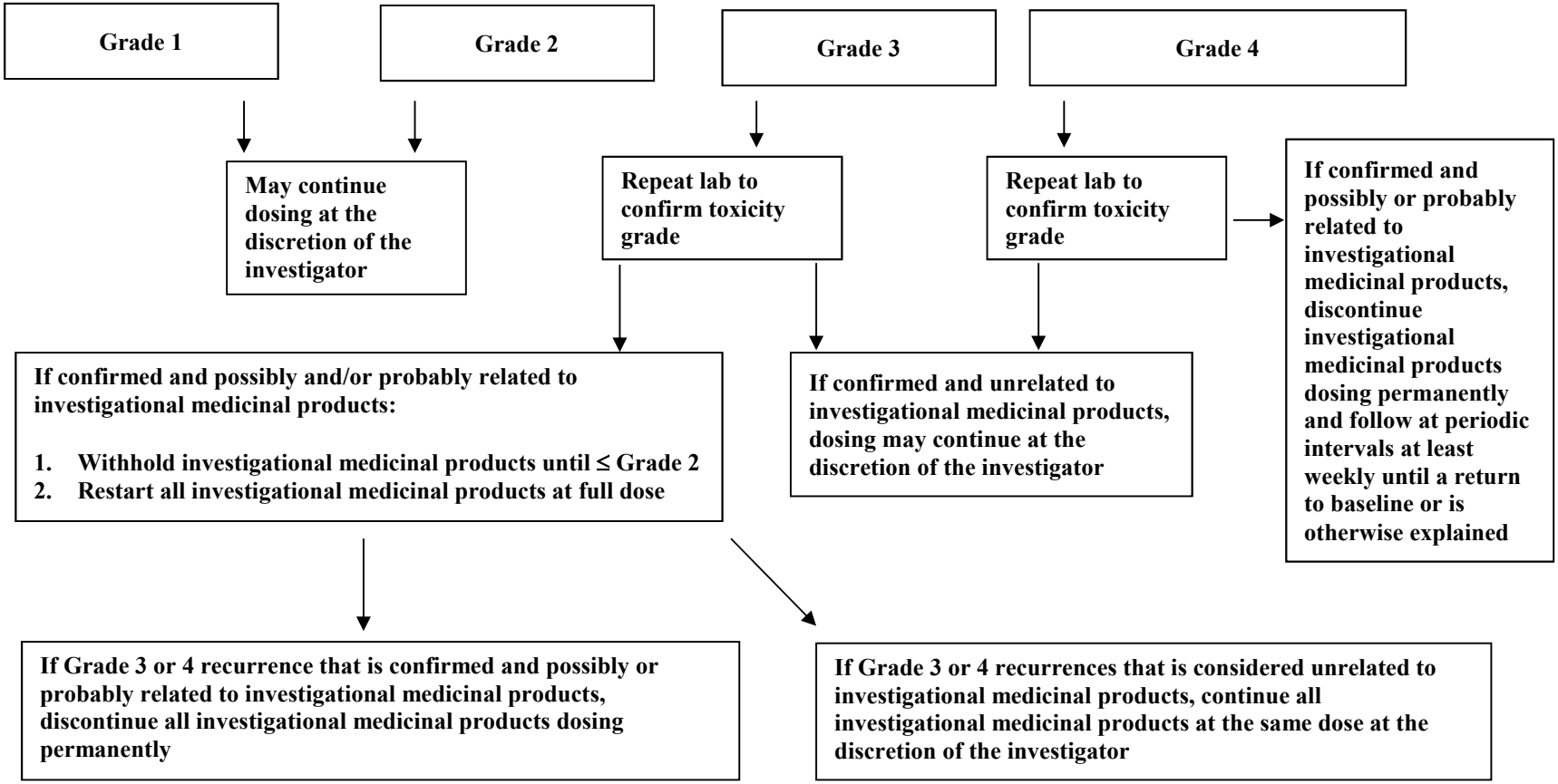
	Screening (−45 Days)	BL	4	4 + 24 Hrs	8	8 + 24 Hrs	12	20	24	36	48	CCI	TFFU[q]
	Visit Windows[a]		± 3 Days										± 7 Days
Imaging Test[n]	X												
CCI													

a The out of visit window is ± 3 days until Week 48, CCI , and ± 7 days for TFFU visits.
b Vital signs include blood pressure, pulse, respiration rate, and temperature.
c The initial DXA will be performed during Screening and should be completed at least 14 days prior to the first dose of study drug. The Week 48 DXA window is – 3 days only. DXA is required for Early Discontinuation (ED) visit if not done within the last 24 weeks.
d It is preferred that subjects take their study drug according to a morning dosing schedule; subjects who elect to dose in the evening the previous day are not required to have in-clinic dosing and provide the single PK sample being collected at Week 4 and 8 visits.
e Serum chemistry and Liver Function Tests: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN). At Baseline, Weeks 24, 48, 96, 144 and 192/ED, subject will be fasting for serum glucose and metabolic panel. Coagulation panel will be done at Screening and then as a reflex only test for ALT flares.
f Qualitative HBsAg and HBeAg will be performed at Screening, Baseline (BL), Weeks 24, 48, 72, 96, 120, 144, 168, 192 and ED. HBeAb and HBsAb testing will be performed as reflex testing as needed.
g Sequence analysis of the HBV pol/RT for possible resistance mutation(s) may be attempted for any subject that experiences viremia (HBV DNA > 69 IU/mL).
h Blood for selected bone biomarkers and renal biomarkers will be collected in a fasted state. Required for ED visit if the last sample was collected > 24 weeks prior.
i Urine for selected renal biomarkers will be collected in a fasted state. Required for ED visit if the last sample was collected > 24 weeks prior.
j For female subjects of childbearing potential, the serum beta-HCG test will be performed at Screening. Urine test will be performed at all other visits as indicated. Positive urine test will be confirmed with serum test. Pregnancy tests should include prevention counseling.
k[j]
l Health Related Quality of Life surveys included in this study are: SF-36, CLDQ, and WPAI. The surveys will be administered at BL, Weeks 24, 48, 96, 144, 192 and Early Discontinuation Visits, if applicable.
m At Weeks 8 and 24 the plasma PK samples should be collected between 15 minutes and 4 hours post-dose.
n At Screening, α-fetoprotein (AFP) will be measured and subjects with an AFP >50 ng/mL or other findings concerning HCC must undergo imaging test (e.g., CT scan) to rule out HCC.
o Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides)
p At Week 48, per Principal Investigator (PI) discretion, subjects will be eligible to receive TAF 25 mg daily CCI
q Subjects who have received at least one dose of TAF and discontinue treatment prematurely CCI will be followed every 4 weeks for 24 weeks off treatment in accordance with TFFU visits or until initiation of alternative CHB therapy, whichever comes first.

Appendix 3. CCI



Appendix 4. Management of Clinical and Laboratory Adverse Events



Appendix 5. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months**[#]	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

An overlap between the Grade 1 scale and the Lab's normal range for absolute neutrophils may result for pediatric subjects. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatermia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L 3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L 2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L 2.0 to < 2.5 mEq/L 2.0 to <2.5 mmolL	< 2.0 mEq/L < 2.0 mmol/L < 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L >ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L > 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L > 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L > 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month** **Infant, < 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bicarbonate **Adult and Pediatric ≥ 4 Years** **Pediatric < 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN NA	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L 11.0 mEq/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L 8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L < 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) Adult	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
LDL (Fasting) Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects > 70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatrics <16 years** **≥ 16 years**	- 3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < LLN g/dL 20 to < LLN g/L 2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L < 2.0 g/dL < 20 g/L	NA NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below				
Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection				
Adult and Pediatric ≥ 10 Years	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24-48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional- symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure – **Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5-20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchiectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Data from clinical pharmacokinetic interaction studies of TAF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Non-clinical toxicity studies in animals (rats and rabbits) of TAF have demonstrated no adverse effect on fertility or embryo-fetal development. However, there are no clinical studies of TAF in pregnant women. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. At minimum, a pregnancy test will be performed at the end of relevant systemic exposure. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following from Screening until the end of relevant systemic exposure.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

  Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of < 1% per year
  - Intrauterine hormone-releasing system (IUS) with a failure rate of < 1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)
  - Barrier methods (one female barrier and one male barrier must be used in combination)
    - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
    - Male barriers: Male condom (with or without spermicide)
  - Hormonal methods
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

3) Contraception Requirements for Male Subjects

During the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.